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Immunomodulatory Action of an Ayurvedic Polyherbal Formulation Maharishi Amrit Kalash-A Scoping Review

Radha Singh [1], Nidhi Kaushik [1], Rini Vohra [1,2*], Richa Shrivastava[3]

[1] *Maharishi Ayurveda Products Private Limited, Noida, Uttar Pradesh-201306, India*

[2] *Maharishi University of Information Technology, Noida, Uttar Pradesh, India*

[3] *Maharishi Ayurveda Europe, B.V, Looskade 20, 6041 LE Roermond, The Netherlands*

Address for Correspondence: Rini Vohra, dr.rini@maharishiayurveda.global

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ABSTRACT: Background: Maharishi Amrit Kalash (MAK) is a polyherbal formulation of Ayurveda with potential immunomodulatory properties. While previous studies have explored its effects, the overall evidence base remains fragmented and inconclusive. This scoping review aims to map the existing literature on MAK, identify research gaps, and inform future research directions to elucidate its potential role in the immune system.

Objective: This scoping review aims to comprehensively identify gaps in current understanding and methodically survey the existing literature on the immunomodulatory effects of Maharishi Amrit Kalash (MAK) through a synthesis of preclinical and clinical studies to provide direction for future research.

Methods: Following PRISMA guidelines, a systematic search of relevant databases was conducted to identify studies investigating MAK's impact on immune function. Inclusion criteria encompassed preclinical and clinical studies evaluating MAK's effects on lymphoproliferative response, and other relevant immune parameters. While research published in other language than English, new reports, unpublished reports were excluded.

Results: A total of 81 studies were found eligible to be reviewed. Out of which only 11 fulfilled the inclusion criteria. Preclinical studies, particularly in murine models, demonstrated enhanced macrophage activity, splenic lymphocyte proliferation, and cytokine production following MAK administration. Clinical trials, including a prospective double-blind, placebo-controlled trial and a study involving 500 individuals, revealed promising outcomes such as significant reductions in allergy symptom scores and improvements in overall well-being, as well as a reduced incidence of colds in the MAK group compared to controls.

Discussion: MAK comes under Rasayana category is recognized for its immunomodulatory properties published in several journals. The preclinical and clinical studies showed that it has promising role in enhancing the macrophage function and lymphoproliferative response that boosts the immunity. Its use over 38 years in several countries also validated its safety and efficacy as an immunomodulatory agent.

Conclusion: The findings of this scoping review highlight the potential of Maharishi Amrit Kalash as an immunomodulatory agent in traditional Ayurvedic medicine. However, further investigation through extensive randomized clinical trials is warranted to conclusively establish its efficacy and safety profile. This review underscores the importance of exploring MAK's immunomodulatory effects in depth to inform clinical practice and public health strategies. © 2024 Caproslaxy Media. All rights reserved.

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INTRODUCTION

The immune system is one of the most intricate biological networks in the human body. Dysregulation of this system underpins a diverse array of pathological conditions, encompassing infectious diseases, chronic inflammatory disorders, and autoimmune ailments [1]. Immunity refers to the body's inherent ability to counteract viral infections by deploying proteins such as interferons and cytokines, which play a critical role in regulating cellular defense and inflammatory responses [2]. These signaling molecules facilitate immune cell mobilization and localized inflammation, both of which are essential for pathogen clearance [3].

With the rapid growth of the global population and increasing life expectancy, there is a heightened need to focus on immune system enhancement as a key public health strategy [4]. Aging is associated with a decline in immune function, making individuals more susceptible to infections and chronic diseases [5]. Therefore, there's a strong need for interventions targeting immunomodulation to address these issues, focusing on using natural drugs with low risks and minimal side effects [6]. Ayurveda, the traditional system of medicine from India, emphasizes strengthening immunity through Rasayana therapy, also known as rejuvenation therapy [7]. This approach is based on well-established principles that enhance the body's innate defense mechanisms against pathogens and environmental stressors. Rasayana herbs possess bioactive properties that support immune regulation, contributing to overall health and resilience against diseases [8].

Several scientific studies have extensively validated the unique properties of Rasayana herbs [9]. Charaka, a key figure in Ayurveda, highlights Rasayana therapy's role in balancing doshas and promoting overall health by mitigating aging and disease-related degeneration [10]. These herbs are well-known for containing specialized metabolites that contribute to immune modulation, antioxidant activities, and the management of neurodegenerative disorders, while also promoting rejuvenation [11]. Maharishi Amrit Kalash (MAK), an Ayurvedic formulation based on the concept of "Brahma Rasayana" is a synergistic blend of 53 herbs and constituents (***Supplementary Table S1***). The combination of Rasayana herbs in MAK enhances its therapeutic potential beyond conventional formulations, making it a comprehensive supplement for rejuvenation and immune enhancement. It is a synergistic blend of Rasayana components that collectively exert heightened therapeutic effects, surpassing the individual contributions of its constituent elements [12]. MAK displayed remarkable antioxidant potential, which was found to be at least 1000 times greater than that of Vitamins C and E [13]. Also, it has been proven in a case study that it has potential to increase the body's oxygen radical absorbance capacity (ORAC value) [14]. The potent antioxidant capability of MAK translates into cell repair, anti-aging effects, reduced inflammation, reduced cytotoxicity, and hence enhanced immunity [15-17].

The therapeutic potential of MAK is firmly established and scientifically validated through 81 comprehensive research studies conducted globally. MAK's Rasayana properties are believed to have an immunomodulatory effect, augmenting the body's resistance to infections, and enhancing longevity without any adverse effects [18,19]. Furthermore, MAK intake supports cellular repair, mitigates brain cell aging, reduces inflammation, and revitalizes organs [20]. It enhances the preparation, activation, responsiveness, and proliferation of T-cells during immune challenges, thereby strengthening defense mechanisms [21]. The cumulative evidence underscores MAK's potential as an efficacious supplement for immune support and overall well-being that includes heart health, chemoprotection in cancer patients and anti- aging effects [22-29]. The study outcomes are clearly presented in the results and discussion sections, highlighting MAK's strong potential in supporting heart health. Scoping reviews provide a descriptive overview of existing literature, helping researchers identify knowledge gaps, map the field, and clarify concepts without critically appraising individual studies or synthesizing evidence [30].

By compiling this information, this review will serve as a foundational resource to support further clinical investigations on immune enhancement across diverse populations, contributing to advancements in healthcare. The objective of this scoping review is to thoroughly document the immunomodulatory effects of MAK, highlight existing gaps, and provide direction for future research.

METHODOLOGY

This scoping review followed the methodological framework established by Arksey and O'Malley. The search strategy was carefully designed in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines to maintain transparency and rigor throughout the process. The final report was structured according to the PRISMA-ScR reporting checklist [30], encompassing six distinct steps (***Supplementary Table S2***). **A**. Initially, the research question was clearly defined to provide a focused direction for the study. **B**. Subsequently, the current body of literature was systematically searched to identify relevant studies pertinent to the research question. **C**. The selection process involved applying predefined inclusion and exclusion criteria to ensure the appropriateness of the chosen studies [31]. **D**. Each selected study was then selected based on predetermined criteria for further analysis. **E**. The data from the included studies were collated, summarized, and reported to present a comprehensive overview of the findings. **F**. Moreover, to enhance the credibility and validity of the results, consultation with domain experts was conducted to validate the findings and interpretations. A risk of bias analysis was also done for both preclinical and clinical studies included in the study based on Cochrane and SYRCLE risk of bias analysis parameters. As part of methodological rigor, an a priori protocol was developed to guide the scoping review process,

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and meticulous documentation was maintained at each stage to ensure reproducibility and transparency [31,32].

A. Formulation of Research Question

To formulate a research question for a scoping review following points were taken into consideration: the population, concept, and context. The research question guiding this scoping review is: What is the role of Maharishi Amrit Kalash (MAK) as an immunomodulator, and what gaps in the current literature need to be addressed to inform future research?

B. Study Identification

A comprehensive search strategy, developed with input from Rini Vohra (RV), was used to identify relevant studies. The search, performed across four selected databases, utilized a combination of keywords and index terms (see ***Supplementary Table S3***). Keywords included "Maharishi Amrit Kalash," "MAK," "MAK-4," "MAK-5," "immunity," "immunomodulation," "illness," and "sickness." To ensure a broad scope, no publication date restrictions were applied. The search process adhered to the PRISMA-ScR guidelines, ensuring methodological rigor and transparency [31].

B.1. Electronic Resources

Six different databases were used for data search: PubMed, Cochrane, AYUSH Research Portal, Google Scholar, Clinical Trials.gov and CTRI. Please see supplementary materials for database search strategies.

B.2. Data Collection and Analysis

Data collection, organization, management, and analysis were facilitated through a combination of tools, each serving a specific purpose. **Google Drive** was utilized as a secure storage platform for all study-related documents and files, ensuring organized and accessible data. **Google Docs** played a crucial role in documentation, allowing real-time collaboration and editing among team members. For data analysis and preparation of evidence tables, **Excel** was employed, providing flexibility in handling and presenting research findings. These tools collectively enhanced the efficiency and effectiveness of the research process.

B.3. Citation Management Process

Duplicate records were eliminated using EndNote and manually (double checked) prior to commencing the review process. Following the screening of all abstracts for inclusion, the remaining studies were transferred to excel sheet for further evaluation.

C. Study Selection

The studies included met the following criteria: publications completed within the time frame; clinical, *in vivo*, and *in vitro* studies; pertinence to immunity and immunomodulation, use of MAK/MAK-4/MAK-5. Both inclusion and exclusion criteria were applied to all studies.

Inclusion criteria were pre-determined in the study protocol. This included the role of MAK in preventing diseases, enhancing lymphocyte proliferation, boosting immunity and immunity markers. In manuscript classification process, it was determined that composition of MAK should be same in every study. Also, the studies on MAK-4, MAK-5 individually or in combination were given equal weightage and were merged under the role of MAK in immunomodulation tag.

Full length manuscripts and abstracts published in English with possible role in boosting the immunity were included in this study. Both preclinical and clinical studies were included. The manuscripts published between 1988-2015 with possible role of MAK in boosting the immunity (directly or indirectly) were included for this review. Publications in the form of case studies, editorials, unpublished literature, testimonials, and letters were excluded.

C.1. Title and Abstract Screening

Abstract screening followed the search and screening strategy to meet the inclusion criteria. Duplicate records were removed prior to title and abstract screening. Two independent reviewers (RS1 and NK) assessed the eligibility of identified studies, with each abstract undergoing dual review. Studies were categorized as "include, (YES)" "exclude, (NO)" or "uncertain (May be)" in an Excel-based evidence table. Studies classified as "uncertain" (May Be) were subjected to group discussion to reach a consensus. Disagreements were resolved through deliberation among the study team or consultation with an Ayurvedic medicine expert. Included studies were detailed in the evidence table for subsequent evaluation.

D. Classification of Studies

Three investigators (NK, RS1, and RV) independently assessed the full-text articles to categorize them based on their focus on immunity. Discrepancies between abstract and full-text content led to the exclusion of certain studies. A predefined categorization system (*in vitro*, *in vivo*, and clinical studies) was employed within an Excel spreadsheet to facilitate data extraction and thematic analysis of the findings.

E. Collating, Summarizing, and Reporting of Results

The results were summarized using descriptive statistics and narrative descriptions. A PICO (detailing Patient Population, Intervention, Comparator, and Outcomes) table was created (**Table 1**) out of the identified research papers focusing on MAK's immunomodulatory activity. While a comprehensive evaluation of the research papers' worth was conducted, one paper was excluded based on predefined criteria.

F. Validation of Results

The results obtained from the classification process underwent validation by experts (RV and RS1), possessing proficiency in herbal medicine, data analysis and in conducting scoping reviews. Recommendations provided by the experts were thoroughly discussed and integrated into the final manuscript.

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Table 1. An evidence table showing the immunomodulatory effect of MAK (PICO Table).

Design	Category	Patient Population/Treatment Groups	Intervention	Outcomes	Conclusion	Type of MAK used	Dosage	Reference
Enhancement of lymphoproliferative response by Maharishi Amrit Kalash in rats.	*In vivo*	Sprague-Dawley rats (220-250 g)	Sprague-Dawley rats weighing between 220-250 g received a daily dose of 50 mg MAK for 20 days. On day 10, the animals were subcutaneously immunized with ovalbumin. On day 21, the splenic lymphoproliferative competence of both groups was assessed using a 3H-thymidine incorporation procedure.	MAK treated animals showed significant enhancement of proliferative response even without the presence of antigen (2-3 folds). The 10-day antibody response showed no difference in both groups.	The increased lymphoproliferative activity suggested MAK may enhance the immune response in rats	MAK-4 & MAK-5	50 mg	[33]
Investigation into the immunomodulatory effect of an Ayurvedic herbal food supplement through priming of splenic lymphocytes.	*In vivo*	Male Sprague Dawley rats wt. approx. 250 g.	Splenic lymphocyte proliferation was assessed by measuring the incorporated radioactivity in both the MAK group (50 mg) and the control group, which were fed standard rodent chow once daily for either 10 or 20 days.	A notable statistical effect was detected upon administering MAK at a dosage of 50 mg/day over periods of 10 or 20 days. This notably boosted the proliferative capacity of splenic lymphocytes. These findings suggest that MAK ingestion did not alter at least two of the studied macrophage functions.	MAK ingestion enhances the production of various cytokines that could promote T-cell receptor expression. MAK can modulate lymphocyte responsiveness while leaving the basal proliferative state unchanged.	MAK-4 & MAK-5	50 mg	[34]
Evaluation of the effects of an Ayurvedic drug on lymphoproliferative response, macrophage-mediated tumor cell killing, and nitric oxide production post-ingestion.	*In vivo*	C57BL/6J male mice.	In this study, five to six mice were randomly assigned to either a control group or a MAK group. Each group was then fed either a standard diet or a diet containing 0.3% MAK for a duration of six weeks. The primary intervention involved investigating the activity of interferon (IFN)-activated macrophages using an 18-hour [^{51}Cr] release assay.	The MAK group showed significantly increased proliferative responses to PHA and anti-CD3 across all concentrations tested. Peritoneal macrophages from this group exhibited enhanced tumor cell killing ability and notably higher levels of nitric oxide (NO) production. These findings suggest that MAK ingestion may induce the *in vivo* production of cytokines such as IL-1, IL-2, or TNF, potentially leading to the expression of the NO synthase gene.	The MAK group demonstrates elevated lymphoproliferative responses to Phytohemagglutinin (PHA) and anti-CD3 antibodies across all concentrations tested. These results indicate that MAK has the potential to induce *in vivo* priming of both T cells and macrophages, resulting in enhanced functional capabilities.	MAK-4 & MAK-5	0.3% w/w	[21]
Immunomodulatory effects of Maharishi Amrit Kalash 4 (M-4) and 5 (M-5) in mice.	*In vivo*	Fifty-three male ddY mice (10 weeks old, initial weights of 33-35g)	Mice received daily oral doses of M-4 and M-5 (50mg/kg or 100mg/kg) for 10 days. Control mice were given water. After 48 hours post-treatment, mice were euthanized for analysis. The study assessed peritoneal macrophage superoxide anion (O-2) production and spleen cell response to concanavalin A (Con A) following M-4 and M-5 administration.	The production of O2 by peritoneal macrophages in the M-5 (50mg/kg) treated group was significantly higher than that in the control group. The indices of spleen cell stimulation by Con A were significantly (3 to 4 times) higher in groups treated with M-4 and M-5 at all doses.	These results indicate that M-4 enhances lymphocyte responsiveness, while M-5 enhances not only lymphocyte responsiveness but also macrophage function. It is also suggested that M-4 and M-5 have mitogenic effects on lymphocytes.	MAK-4 & MAK-5	50mg/kg, 100 mg/kg	[35]
Investigation of effect of Amrit Kalash 4 (MAK-4) in enhancing immune function in male A/He mice.	*In vivo*	Forty-eight male A/He mice weighed 19-20g aged 7 weeks	Animals were randomly divided into 4 groups (12 each). Nitric oxide (NO) production by peritoneal macrophages and proliferation of spleen cells stimulated by mitogens were examined in mice. The mice received MAK-4 via gastric intubation at dosages of 10, 50, and	Glucose consumption of peritoneal macrophages ($p<0.05$), lactate dehydrogenase activities ($p<0.01$), and macrophage production of NO stimulated by lipopolysaccharide ($p<0.01$) were significantly higher at all doses of MAK-4.	These results indicated MAK-4 enhances not only macrophage function but also lymphocyte responsiveness in mice.	MAK-4	10mg/kg, 50mg/kg and 100mg/kg	[36]

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			100mg/kg once daily for 20 days.	Additionally, splenocyte production of interleukin-2 ($p<0.01$) was significantly higher in the MAK group. Among MAK-4 treated mice, those receiving the dose of 10 mg/kg exhibited the highest IL-2 production by splenocytes.				
Evaluation of dose-effects of Maharishi Amrit Kalash 4 (MAK-4) on the immune function in female inbred BALB/c mice.	*In vivo*	Sixty BALB/c female mice (10 weeks old, initial weights of 17-18g)	Mice were randomly divided into 5 groups (12 mice/ group) to investigate the effect of MAK on superoxide anion (O2-), production of peritoneal macrophages and the response of spleen cells to concanavalin A (Con A) in mice administered with MAK-4 by gastric intubation of an aqueous emulsion at the dose of 10, 50, 100 or 200 mg/kg once a day for 20 days.	Glucose consumption by peritoneal macrophages in MAK-4-treated mice at 10 and 50 mg/kg doses, after both 24 and 48 hours, was significantly higher than the control. However, at 100 and 200 mg/kg doses after 48 hours, it was significantly lower. O2 production without stimulation increased at 10 and 50 mg/kg but decreased at 100 and 200 mg/kg. Acid phosphatase levels decreased, while β-glucuronidase and lactate dehydrogenase activities increased at lower doses. However, at higher doses, they decreased. MAK-4 did not enhance spontaneous splenic lymphocyte proliferation, but stimulation indices were significantly higher in all MAK-4-treated groups.	Doses of 10 and 50 mg/kg per day appear to be suitable for enhancing both macrophage function and lymphocyte responsiveness following gastric intubation of MAK-4 in mice.	MAK-4	10mg/kg, 50mg/kg. 100mg/kg or 200 mg/kg	[37]
Dose-dependent activation of immune function in mice by ingestion of Maharishi Amrit Kalash- 5 (MAK-5)	*In vivo*	Sixty BALB/c female mice (10 weeks old, initial weights of 17-18g)	The study involved randomly assigning mice into five groups. Superoxide anion (O2-) production by peritoneal macrophages and spleen cell response to concanavalin A (Con A) were assessed. Mice received MAK-5 at doses of 10, 50, 100, or 200 mg/kg once daily for 20 days. Glucose consumption by peritoneal macrophages was also monitored.	Glucose consumption by peritoneal macrophages in MAK-5-treated mice was notably higher at all doses after 24 hours, and at 200 mg/kg after 48 hours. O2-production with a stimulator was significantly elevated at 200 mg/kg. Activities of β-glucuronidase and lactate dehydrogenase increased across all doses. While MAK-5 didn't enhance spontaneous splenic lymphocyte proliferation, stimulation indices were notably higher at 50, 100, and 200 mg/kg doses.	MAK-5 once a day at the dose of 50 mg/kg enhances not only macrophage function but also lymphocyte responsiveness in mice.	MAK-5	50, 100, and 200 mg/kg	[38]
Modifying Effects of Maharishi Amrit Kalash (MAK-4 and MAK- 5) on Phagocytic and Digestive Functions of Macrophages in	*In vivo*	Sixty male ICR mice, 3 weeks old, weighing 10 to 12 g	Sixty male ICR mice aged 4 weeks were divided into three groups: control (no treatment), MAK-4-treated, and MAK-5-treated. MAK-4 and MAK-5 were administered orally at 50 mg/kg per day (5 days/week) for 7 weeks. Phagocytic activity was assessed by measuring the clearance of colloidal carbon from peripheral blood.	MAK-4 and MAK-5 treatment enhanced the phagocytic function of the reticuloendothelial system, as evaluated by carbon clearance. Both MAK-4 and MAK-5 groups exhibited a significant increase in superoxide anion (O2-) production by peritoneal macrophages. Acid phosphatase activity significantly	The long-term administration of MAK-4 and MAK-5 enhances macrophage phagocytic and digestive functions, representing a primary stage of host defence. This is supported by increased O2-production capacity and enzyme activity in peritoneal macrophages in mice.	MAK-4 & MAK-5	50mg/kg	[39]

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Male ICR Mice.				increased in the MAK 4 group but not in the MAK 5 group. Activities of β-glucuronidase and lactate dehydrogenase significantly increased in both MAK 4 and MAK 5 groups compared to controls.				
Effects of Maharishi Amrit Kalash 5(MAK-5) on immune functions in aged mice	*In vivo*	Specific pathogen-free (SPF) inbred male C3H/He N mice. Young mice (2 months old, weighing 24 to 26 g, n = 10) and old mice (22 months old, weighing 30 to 34 g, n = 40) w	Male C3H/He N mice were categorized into five groups: two control groups with no treatment (old control: 22-month-old and young control: 2-month-old), and three groups treated with varying doses of MAK-5. MAK-5 was orally administered at 50 mg/kg, 100 mg/kg, or 200 mg/kg per day, three days a week, for a duration of two months.	Old mice treated with all doses of MAK-5 showed significantly higher glucose consumption in peritoneal macrophages after 48 and 72 hours. Nitric oxide production stimulated by lipopolysaccharide (LPS) was notably higher in old mice treated with MAK-5 compared to controls, but not versus young controls. Stimulation index (S.I.) and cytokine production (IL-2, IFN-γ, IL-4) were significantly elevated in MAK-5-treated old mice compared to controls.	The findings indicate that MAK-5 mitigated the age-related decline in glucose consumption by peritoneal macrophages and attenuated the reduction in cellular immune function, suggesting its potential role in preventing immunosenescence.	MAK-5	50 mg/kg, 100 mg/kg, or 200 mg/kg	[40]
A double-blind randomised placebo-controlled trial of MAK-5 in the management of seasonal respiratory allergy (hay fever).	Clinical study	Forty-six people	The main variable studied was allergy symptoms, assessed through a daily diary recording the duration of primary rhinitis symptoms: sneezing, stuffy or runny nose, redness, itching, watery eyes, coughing, and medication use. Subjects were paired based on sex, age, and symptom severity during a one-week baseline period in mid-May. They were then randomly assigned to either the placebo or MAK-5 group. Patients in both groups recorded their allergy symptoms and use of conventional anti-allergy medications.	One tailed t- test on log symptom scores showed significant differences during three of four experimental weeks, with lower mean allergy symptom scores in the MAK group (week 1: p=0.014, week2: p=0.097, week3: p=0.025, week4: p=0.025) There were no difference at baseline(p=0.115).	MAK-5 reduces symptoms of seasonal respiratory allergies, with the most notable difference observed during the initial week, coinciding with the highest pollen counts and the most severe symptoms recorded.	MAK-5	1000 mg/day	[20]
Prospective study of health improvements in users of Maharishi Amrit Kalash 5 (MAK-5).	Observational study	500 people	First-time users of MAK-5 were surveyed regarding their general well-being and chronic medical problems. Questionnaires using a Likert scale were sent to 500 individuals, with a 78% response rate. A second questionnaire was mailed 75 days after receiving the tablets, with a 55% response rate, resulting in a complete response rate of 43%. Users did not have access to their previous responses, serving as their own controls.	Statistically significant increases were observed in psychological well-being ($p<0.03$) and alertness in daily activity ($p<0.03$), along with improvements in various common disorders including headaches ($p<0.01$), backaches ($p<0.01$), sinus congestion ($p<.01$), difficulty digesting meals ($p<0.01$), underweight ($p<0.01$), and anxiety ($p<0.03$). Additionally, subjects reported fewer colds (mean=0.19) during the two months of taking MAK compared to the previous two months ($p<0.01$). A trend towards improvement ($p<0.1$) was noted in overall physical health and muscle and joint stiffness.	This study provides support for the hypothesis that MAK-5 may act as an immune modulator or improve general physiological homeostasis.	MAK-5	1000mg/day	[22]

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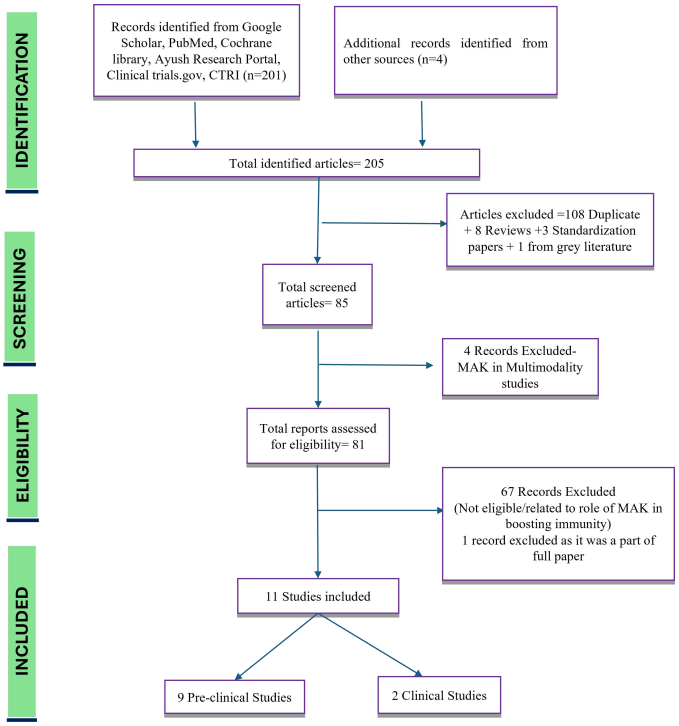

Figure 1. PRISMA flow chart.

RESULTS

This review included eleven studies spanning preclinical and clinical research (**Figure 1**). Nine investigations were conducted at the preclinical level, while two were clinical trials. The included literature represented a diverse range of study designs.

The focus of the research varied. Five studies evaluated the combined efficacy of MAK-4 and MAK-5, while four specifically investigated MAK 5. A single study investigated the effects of MAK-4 alone. The geographic distribution of these studies was global, including the research conducted in Japan, the United States, and India. The temporal scope of the included literature extended from 1988 to 2015.

Collectively, the findings from both preclinical and clinical studies suggest a potential immunomodulatory role for MAK. However, given the heterogeneity of study designs and outcomes, further rigorous investigation is warranted to elucidate the precise mechanisms of action and clinical implications of these observations.

A. Preclinical Studies

The initial investigation into MAK, was conducted by Patel et al., in 1988, demonstrated its capacity to augment lymphoproliferative reactions in Sprague Dawley rats [33]. The immunological mechanism underlying MAK was elucidated by noting that the antibody response measured via the haemagglutination test after 10 days was similar between the phytohemagglutinin (PHA) treated and untreated groups of rats. Specifically, administering 50g of MAK to these rats over twenty days resulted in a significant increase in lymphocyte proliferation, both in the presence and absence of ovalbumin, by at least twofold. This enhanced proliferation was comparable to the response elicited by Phytohemagglutinin; a well-established mitogen used to stimulate lymphocyte proliferation [33].

Dileepan et al. (1990) conducted a study on male Sprague Dawley rats to evaluate the impact of MAK-5 on immune function. The researchers measured mitogen-induced lymphocyte proliferation, macrophage superoxide anion production, and phagocytosis. Results indicated a significant enhancement in lymphocyte proliferative responses to PHA (enhanced to 32-88%), Concanavalin A (Con A), and pokeweed mitogen following MAK-5 ingestion. This effect persisted for at least 15 days post-treatment. Notably, MAK-5 did not influence spontaneous lymphocyte proliferation or macrophage function [34].

In 1993, Dileepan and colleagues investigated the effects of MAK on enhancing immune responses in C57BL/6J mice. Their study demonstrated that lymphocytes from mice fed with MAK exhibited significantly higher proliferative responses to PHA and anti-CD3 compared to controls, in a dose-dependent manner. Furthermore, peritoneal macrophages from MAK-fed mice displayed enhanced tumour cell killing when activated with lipopolysaccharide (LPS) and interferon-gamma (IFN-γ), or a combination of LPS and IFN. Additionally, the production of nitric oxide (NO) by macrophages activated with LPS or IFN from MAK-treated mice was notably higher than in controls. Importantly, neither the cytotoxicity nor the NO production by inactivated macrophages was affected by MAK supplementation. These results indicate that MAK contains ingredients capable of priming both T cells and macrophages *in vivo*, resulting in enhanced immune functions [34].

Another investigation examined the impact of MAK-4 and MAK-5 on the O_2 production by peritoneal macrophages, indicative of macrophage functions, and on the Con A-induced mitogenic response of spleen cells, a marker for lymphocyte functions in mice. The MAK-5 (50mg/kg) treated group displayed notably elevated production of peritoneal macrophages compared to the control group. Furthermore, groups treated with MAK- 4 and MAK- 5 at all doses exhibited significantly increased stimulation indices of spleen cells by Con A (3 to 4 times higher) compared to the control group. These findings suggest that MAK-4 enhances lymphocyte responsiveness, whereas MAK-5 not only enhances lymphocyte responsiveness but also boosts macrophage function. Additionally, the study suggests potential mitogenic effects of MAK-4 and MAK-5 on lymphocytes [35]. This effect was further validated in a study conducted by Inaba et al., 1996, that showed the effect of MAK-4 on the NO production by peritoneal macrophage function and the mitogenic response of spleen cells as an indicator of lymphocyte function in 7 weeks old male A/He mice [36]. The results showed that gastric intubation of MAK-4 once a day at the dose of 10mg/kg enhances not only macrophage's function but also lymphoproliferative responsiveness in mice. The glucose consumption of peritoneal macrophage during incubation up to 72hr at all doses of MAK-4 was significantly higher in MAK group Activities of lactate dehydrogenase in the peritoneal macrophage and the macrophage production of NO stimulated by lipopolysaccharide were significantly increased in MAK-4

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treated mice as compared to the control mice (P<0.01). Also, stimulation indices of both Con A and PHA were higher in MAK group than control. In addition, the splenocyte production of interleukin-2 stimulated by Con A was higher in MAK group (maximum production of IL-2 in mice fed with 10mg/kg MAK-4) [36].

In 1997, Inaba and colleagues [37,38] conducted two separate studies on female BALB/c mice to assess the effects of MAK-4 and MAK-5 ingestion at doses of 10, 50, 100, or 200 mg/kg once daily for 20 days. They examined superoxide anion (O2-) production by peritoneal macrophages and the spleen cells' response to Con A. The findings mirrored earlier results as discussed above [36], revealing that MAK-4 treatment at 10 and 50 mg/kg significantly increased glucose consumption by peritoneal macrophages after both 24 and 48 hours, while at 100 and 200 mg/kg, it decreased after 48 hours. O2 production without a stimulator was enhanced at 10 and 50 mg/kg, whereas with a stimulator, it was higher at these doses but lower at 100 and 200 mg/kg compared to controls. Acid phosphatase activity decreased at 100 and 200 mg/kg, while β-glucuronidase (GLU) and lactate dehydrogenase (LDH) activities increased at 10 and 50 mg/kg but decreased at 100 and 200 mg/kg. MAK-4 didn't boost spontaneous splenic lymphocyte proliferation but increased stimulation indices at all doses [37]. Similarly, MAK-5 treatment led to significantly higher glucose consumption in peritoneal macrophages at all doses after 24 hours and only at 200 mg/kg after 48 hours. O2- production with a stimulator was significantly higher at 200 mg/kg. GLU and LDH activities were elevated at all doses, while spontaneous splenic lymphocyte proliferation wasn't affected. Stimulation indices were significantly higher at 50, 100, and 200 mg/kg [38].

The effect of MAK-4 and MAK-5 was also investigated on phagocytic and digestive functions of macrophages in male ICR mice [39]. The phagocytic function of the reticuloendothelial system, assessed by carbon clearance, was enhanced by both MAK-4 and MAK-5 treatments. Additionally, there was a significant increase in superoxide anion (O2-) production by peritoneal macrophages in both MAK-4 and MAK-5 groups. While MAK-4 treatment significantly increased acid phosphatase activity in peritoneal macrophages compared to the control group, this effect was not observed in the MAK-5 group. Moreover, the activities of β-glucuronidase and lactate dehydrogenase were significantly elevated in both MAK-4 and MAK-5 groups compared to the control group [39].

Inaba et al., 2005, demonstrated that MAK-5 suppressed age-associated glucose consumption by peritoneal macrophages and reduced cellular immune function, indicating its potential contribution to the prevention of immunosenescence. In this study old mice treated with MAK-5 at all doses showed significantly increased glucose consumption by peritoneal macrophages after 48 and 72 hr of incubation compared to controls group (no treatment group). Nitric oxide production by peritoneal macrophages stimulated by LPS was significantly higher in old mice treated with MAK-5 at all doses compared to the old control group but not compared to the young control group. Stimulation index was significantly higher in old mice administered MAK-5 at all doses (50 mg/kg, 100 mg/kg or 200 mg/kg per day (3 days/ week) for 2 months). IL-2 production stimulated by Con A was significantly higher in old mice treated with MAK-5 at all doses. IFN-γ production stimulated by Con A was significantly higher in old mice given MAK-5 at doses of 100 mg/kg and 200 mg/kg. Additionally, IL-4 production by splenic lymphocytes stimulated by Con A was significantly higher in old mice treated with MAK-5 at doses of 100 and 200 mg/kg [40].

B. Clinical Studies

The preclinical studies lay a strong foundation for understanding the benefits of MAK in immunity. However, preceding these studies, two observational studies also suggested the MAK's role as an immunomodulator.

In a prospective double-blind and placebo-controlled trial by Glaser in 1991, forty-six subjects were pair-matched for sex, age, and severity of symptoms during a one-week baseline period in mid-May. They were randomized into placebo and MAK-5 groups, with both groups continuing to record their symptoms and medication in diaries for a one-month period [18]. A one-tailed t-test on log symptom scores showed significant differences during three of the four experimental weeks (the period when the highest pollen counts and greatest symptom severity were recorded), with lower mean allergy symptom scores in the MAK-5 group (week 1: p=0.014, week 2: p=0.097, week 3: 0.025, week 4: 0.025). There was no difference at baseline (P=0.115) [20].

In another prospective study conducted on 500 individuals (mean age 40 years and 62% males) for general well-being and common chronic medical problems using a Likert scale from 0 to 4, improvements were noted in mean pre-to-post differences on all 20 measures studied. During the two months subjects took MAK, they had fewer colds (mean=0.19) than during the previous two months (mean=0.39), p<0.01. A trend toward improvement (p<0.1) was found in overall physical health and muscle and joint stiffness. Also, significant increases in physiological well-being with P<0.3, as well as improvements in common disorders like headache, backache, sinus congestion, difficulty digesting meals, underweight, and anxiety were observed. This study supports the hypothesis that MAK-5 may be effective as an immunomodulator or in improving general physiological homeostasis [22]. All the clinjcal trials conducted on MAK were conducted with proper consent of subjects and with due permission of the ethical committee and under regulatory acceptable conditions.

C. Risk of Bias Assessments of the Studies

The risk of bias assessment for preclinical studies are presented in **Table 2.**

Two clinical studies included in this study showed low risk of selection bias. There was low bias in blinding of participants in the study conducted by Glaser et al., 1991b [22] and high risk for Glaser et al 1991a [20]. Detection bias was rated low in both the studies. Attrition bias was rated unclear for all studies. The risk of bias regarding reporting bias was low in both the cases while unclear in other sources of bias category.

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D. Possible Mechanism of Action for Immunomodulatory Effects of MAK

Macrophages are pivotal in immune regulation, performing various functions such as antigen presentation, bacterial and tumour cell killing, and cytokine production [41]. They clear pathogens through phagocytosis and produce reactive oxygen species for defence. Serving as antigen-presenting cells (APCs), macrophages play a vital role in immunity by engulfing, processing, and presenting foreign substances to lymphocytes [42]. This process stimulates T lymphocytes to release interleukin-2 (IL-2), orchestrating lymphocyte activation and proliferation, thus initiating and amplifying the immune response. The findings from multiple studies collectively suggest that both MAK-4 and MAK-5 possess properties capable of enhancing macrophage and lymphocyte functions, potentially bolstering the body's immune response [21,34,35].

Table 2. Risk of Bias assessment using SYRCLE's risk of bias tool.

	Dileepan et al., 1993 [21]	**Patel et al., 1988 [33]**	**Dileepan et al., 1990 [34]**	**Inaba et al., 1995 [35]**	**Inaba et al., 1996 [36]**	**Inaba et al., 1997a [37]**	**Inaba et al., 1997 b [38]**	**Sugiura et al., 1998 [39]**	**Inaba et al., 2005 [40]**
1. Sequence Generation (Selection Bias)	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
2. Baseline Characteristics (Selection Bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
3. Allocation Concealment (Selection Bias)	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
4. Random Housing (Performance Bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
5. Blinding of Investigators (Performance Bias)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
6. Random Outcome Assessment (Detection Bias)	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
7. Blinding of Outcome Assessor (Detection Bias)	Unclear	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear	Low risk
8. Incomplete Outcome Data (Attrition Bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
9. Selective Reporting (Reporting Bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
10. Other Sources of Bias	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear	Low risk

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D.1 Priming of T-Cells and Macrophages: MAK ingestion induces a phenomenon known as *in vivo* priming of both T cells and macrophages. The increased lymphocyte proliferation is dose-dependent on the mitogen and persists for up to two weeks post-MAK withdrawal, indicating *in vivo* priming [21,34]. This process enhances their functions, such as antigen presentation, phagocytosis, and cytokine production [43]. By priming these immune cells, MAK prepares them to respond more effectively to subsequent immune challenges.

D.2 Mitogenic Effects: Both MAK-4 and MAK-5 exhibit mitogenic effects on lymphocytes. This means that they stimulate the proliferation and activation of lymphocytes, particularly T-cells [44]. This stimulation may involve the augmentation of cytokine production, such as interleukins, which are essential for T-cell activation and proliferation. Research has shown that lectins present in plants like Mudgaparni (*Phaseolus trilobus*), one of the main ingredients in MAK can prompt lymphocyte transformation and proliferation in laboratory settings [45,46]. Moreover, various other lectins and alkaloids with similar mitogenic effects have been discovered [47-49]. Considering the diverse composition of MAK, which include herbs and minerals, it's plausible that they may also contain such mitogenic substances.

D.3 Macrophage Function Enhancement:

a. *Phagocytic and Digestive Functions*: Long-term administration of MAK-4 and MAK-5 enhances the ability of macrophages to engulf and digest foreign substances including pathogenic bacteria. This enhancement is demonstrated by increased production of reactive oxygen species (O2-) and the activity of lysosomal and cytoplasmic enzymes in peritoneal macrophages [37,38]. This property of MAK is directly correlated with its antimicrobial activity and could be a possible mechanism behind the role of MAK in improving innate immunity [50,51].

b. *Activation of Pentose Phosphate Pathway*: MAK-4 and MAK-5 activate the pentose phosphate pathway in peritoneal macrophages [39]. This metabolic pathway is crucial for providing energy and reducing equivalents necessary for various cellular functions, including immune responses [52], variations in macrophage metabolic processes, such as glucose uptake, mitochondrial function, amino acid uptake, and lipid synthesis, correlate with changes in cytokine production and phagocytic activity [53]. For instance, the pentose phosphate pathway (PPP) is upregulated to maintain NADPH levels during acute oxidative stress. Lipopolysaccharide-stimulated macrophages increase ROS production via NADPH and NOX activation through PPP induction [54]. However exact mechanism behind generation of NADPH in macrophages is unclear.

D.4 Antitumor Activity:

a. *Enhanced Macrophage Function*: MAK treatment increases the functionality of macrophages, making them more effective in recognizing and eliminating tumor cells [33]. This enhanced function is evidenced by increased glucose consumption and production of nitric oxide (NO2-) in response to activating triggers like LPS and IFN-γ [55,56].

b. *Cytokine Production:* MAK-5 boosts the production of key cytokines, including IL-2, IFN-γ, and IL-4. These cytokines are vital for regulating immune responses, including antitumor immunity, and restoring immune balance in aging individuals. These findings correlate with the broader understanding of cytokines' role in bridging innate immunity, inflammation, and cancer [46].

D.5 Enhancement of Lysosomal Immunomodulatory Function:

Recent researches reported that after the activation of macrophages in the priming stage, activities of lysosomes increase [57]. Lysosomal enzymes such as aminoglycoside phosphotransferase (APH) and β-glucuronidase (GLU), and cytoplasmic enzymes such as LDH and GOT in the macrophages were increased [58]. This property might lead to following functions:

a. *Lymphocyte Proliferation:* Both MAK-4 and MAK-5 may stimulate the proliferation of murine lymphocytes [33,34,38]. This stimulation could involve the production of various cytokines and modulation of T-cell receptor expression, ultimately leading to enhanced immune responses [59].

b. *Enhancement of Cytokine Production*: MAK ingestion may enhance the production of cytokines from both Th1 and Th2 cells (helper T cells). This broad cytokine production profile suggests that MAK has the potential to modulate immune responses by influencing the balance between different subsets of T helper cells. It suggests that MAK-4 and MAK-5 can induce peritoneal macrophages to phagocytose foreign substances [37,38].

E. Safety

None of the included studies recorded adverse events, and no contraindications for MAK-4, MAK-5, or their combination (MAK-4 + MAK-5) have been reported in any studies conducted to date. This aligns with the long history of safe use of MAK in Ayurveda. Furthermore, clinical trials have indicated good acceptance of its taste and texture, with high compliance observed throughout study periods. These findings highlight the diverse immunomodulatory effects of MAK-4 and MAK-5, including their ability to enhance macrophage and lymphocyte functions, exert antitumor activity, and potentially restore immune balance in aged individuals. However, given the long-term use of MAK, a more detailed evaluation of its safety profile including potential risks, contraindications, and interactions would be valuable in future research.

DISCUSSION

This scoping review systematically examined the available literature on MAK, encompassing both preclinical and clinical studies conducted globally between 1988 and 2005. By synthesizing findings from diverse study designs, this review aimed to elucidate the potential immunomodulatory effects of MAK and guide for future research directions.

A. Summary of Evidence

This scoping review represents the first-ever attempt to explore the direct role of MAK in enhancing immunity. Most of the evidence comes from preclinical studies, which suggest

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that MAK significantly enhances the lymphoproliferative response. Two clinical studies demonstrated that MAK increases resistance to illness and improves overall health in a population of 500 individuals. These clinical findings complement other randomized controlled trials (RCTs) on the effects of MAK in promoting heart health, mental well-being, and chemotoxicity prevention. A recent scoping review also highlighted its role in improving cancer patients' quality of life during chemotherapy, while a systematic review confirmed its benefits through standard RCTs.

Qualitative and quantitative analyses identified potent antioxidants in MAK, such as flavonoids and terpenoids, which contribute to immune defense. This antioxidant effect was further validated in a case study by Zanella et al. (2015) [14], showing reduced oxidative stress in patients following MAK supplementation, both short-term and long-term.In vivo studies on rat models showed a significant enhancement in the lymphoproliferative response. Notably, animal studies confirmed that MAK improves macrophage function, aiding in neutralizing foreign particles. This finding supports clinical observations that individuals prone to pollen allergies were not affected after using MAK, even during peak pollen seasons. While the clinical trials included in this review are observational and based on subjective parameters, they support preclinical findings. However, no clinical trial has yet quantitatively demonstrated (via serological tests) MAK's immunomodulatory effects via serological tests. Therefore, further research is needed to establish MAK's role as an immunomodulator.

Rasayana therapy is key component of Ayurveda and traditional, complementary, and integrative medicine, aimed at alleviating diseases by enhancing the body's defense mechanisms and overall immunity. MAK, an Ayurvedic Rasayana formulation, restores balance in Rasa (fluids) and Dhatus (tissues), promoting Ojas, the vital energy supporting immune resilience. Comprising 53 herbs, including Rasayana-class botanicals like Amla, Ashwagandha, Mandukparni, and Yashtimadhu, MAK synergistically boosts immunity.
Its antioxidant properties help defend against illnesses, while phytochemicals such as phenols, flavonoids, and tocopherols further strengthen immune function.

Hence, it can be postulated that MAK could serve as a valuable therapeutic complement when combined with other traditional and complementary medicine practices.

B. Heterogeneity in Study Designs and Its Implications

A key challenge in drawing definitive conclusions from this scoping review is the heterogeneity in study designs, methodologies, and measured outcomes across the included studies. This variation introduces complexity in comparing findings and establishing uniform conclusions about MAK's immunomodulatory potential. The heterogeneity in MAK studies arises from variations in preclinical models, clinical study designs, formulations, treatment durations, and the absence of large-scale RCTs. Preclinical studies used different animal models and assessed diverse immune parameters, making comparisons difficult. Clinical studies varied in methodology, with some relying on subjective measures and others on specific immune endpoints, lacking standardized biomarkers. Different MAK formulations with distinct herbal compositions further contributed to inconsistent findings. Variability in treatment duration and follow-up periods complicates long-term immune benefit assessments. While preclinical studies provide strong mechanistic insights, clinical validation remains limited due to the absence of large-scale, multi-center RCTs. Future trials with standardized immune markers, serological assessments, and objective clinical endpoints are needed to substantiate the preliminary findings.

LIMITATION AND RECOMMENDATION

Research on Maharishi Amrit Kalash (MAK) provides valuable insights into its immunomodulatory effects, yet several limitations must be considered. the findings may not directly translate to human physiology, necessitating caution in extrapolation. Additionally, studies indicate dose-dependent effects of MAK, emphasizing the need for optimized dosage regimens to balance therapeutic benefits and potential side effects. Despite promising preclinical findings, robust clinical evidence supporting the efficacy of MAK in humans is lacking, highlighting a critical knowledge gap. Mechanistic understanding of how MAK interacts with the immune system remains incomplete, necessitating further research to elucidate underlying pathways.

Future research should prioritize well-designed clinical trials to validate preclinical findings and assess safety and efficacy in human populations..

This scoping review is the first to comprehensively examine MAK's immunomodulatory effects employing an extensive search strategy. Despite including clinical trial registries and gray literature, we found a notable shortage of high-quality RCTs on MAK's immunomodulatory properties. Systematic studies, including placebo-controlled blinded trials and biochemical analyses using advanced techniques like mass spectrometry, are essential for identifying specific pathways targeted by MAK.

Long-term clinical trials, observational cohort studies, and RCTs are needed to evaluate MAK's safety profile over extended periods. These studies should identify potential adverse effects associated with prolonged use and ensure more reliable outcomes. Population-specific studies can further elucidate variations in response across demographic groups. Addressing these limitations and implementing these recommendations will advance our understanding of MAK's role in immune modulation and human health. Characterizing its active principles and unraveling its mode of action remain crucial, given MAK's potential as an immunomodulator.

CONCLUSION

Maharishi Amrit Kalash (MAK) exhibits a broad spectrum of immunomodulatory effects, supported by both preclinical and clinical studies. Animal models consistently demonstrate MAK's ability to enhance macrophage and lymphocyte functions, including increased lymphocyte proliferation, enhanced macrophage activity, and elevated cytokine

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production. These findings suggest MAK's potential in strengthening immune responses, exhibiting antitumor properties, and addressing immune imbalances associated with aging.

Clinical trials further support MAK's immunomodulatory benefits, showing improvements in allergy symptoms, overall well-being, and physiological balance. However, current research remains limited by its reliance on animal models, emphasizing the need for more comprehensive clinical evidence in human subjects. Additionally, a deeper understanding of MAK's mechanisms within the immune system is crucial, requiring further investigation into its underlying pathways.

SUPPLEMENTARY FILES

The supplementary file contains a comprehensive list of ingredients found in MAK, along with the sources utilized to gather information for the preparation of the scoping review. Download it from the journal website.

LIST OF ABBREVIATIONS

MAK: Maharishi Amrit Kalash
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PHA: Phytohemagglutinin
ConA: Concanavalin A
LPS: Lipopolysachharide
β-GLU: Beta Glucorinidase
LDH: Lactate dehydrogenase
APCs: Antigen presenting cells
PPP: Pentose phosphate pathway
NADPH: Nicotinamide adenine dinucleotide phosphate hydrogen
ROS: Reactive oxygen species
NOX: Nitrous oxide radical

DECLARATIONS

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. The Journal and Publisher will not be responsible for any copyright infringement or plagiarism issues.

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AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: **Conceptualization**: Radha Singh (RS1), Nidhi Kaushik (NK); **Data curation**: NK, RS1; **Formal Analysis**: RS1, Rini Vohra (RV); **Funding acquisition**: Not Applicable; **Investigation**: NK, RS1; **Methodology**: RS1, NK **Project administration**: RV; **Resources:** Maharishi Ayurveda Products Private Limited; **Software**: Microsoft excel; **Supervision:** RV, Richa Shrivastava (RS2); **Validation**: RS1, RV; **Visualization:**RV1, RS1, NK; **Writing- original draft:** NK, RS1; **review & editing**: RS1, RV and RS2.

CONFLICT OF INTEREST

The authors of this manuscript declare no conflict of interest.

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DATA AVAILABILITY

All relevant data supporting the findings of this study are included in the article and its supplementary materials

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