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A scoping review on 'Maharishi Amrit Kalash', an ayurveda formulation for cancer prevention and management

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ABSTRACT

Background: Cancer is one of the leading causes of morbidity and mortality. Current treatments include chemotherapy, radiotherapy, etc., are known to be associated with several side effects. Hence, complementary and alternative medicine is growing in acceptance around the world, particularly Ayurvedic formulations. MAK is one of the most scientifically acclaimed formulations with potential anti-neoplastic and chemoprotective properties.

Objective: To study literature available on the anti-neoplastic and chemoprotective effects of MAK.

Material and methods: A systematic literature review was conducted using multiple web-based sources: Google Scholar (185), PubMed (33), DHARA (49), AYUSH research portal (2), EBSCO (66), and CTRI (1) for all studies published before February 2021 using keywords: *Maharishi Amrit Kalash, Amrit Kalash, Amrit, MAK-4, MAK-5, MAK-7,* and others. A manual search was conducted on the reference list of all included articles to identify additional studies. Studies with cancer and/or chemotoxicity outcomes were selected manually. Evidence from both preclinical and clinical level studies have been included in the current review.

Results: Out of total 79 studies on applications of MAK, 13 studies were found to state its anti-neoplastic and chemoprotective effects. The studies showed role of MAK in initiation of neoplastic transformation of cancer cells (1), carcinogenesis inhibition (4), metastases inhibition/reduction (1), cancer growth inhibition (4), induction of morphological and biochemical differentiation of cancer cells (3), and reduction in chemotoxicity (4). In studies with controlled clinical trial design (3), MAK use among patients with cancer showed a significant reduction in anorexia, vomiting, and other side effects associated with chemotherapy. A general improvement in quality-of-life scores (Karnofsky Performance Status) and well-being was also observed among patients using MAK.

Conclusion: Evidence from pre-clinical studies show promising results for use of MAK as an anti-cancer and a chemoprotective agent. More clinical studies are needed to assess the impact of MAK use for tumour regression among patients with cancer. Current scoping review provides sufficient evidence on MAK to be considered for further exploration for its anti-cancer/chemoprotective effects in bigger randomized clinical trials.

1. Introduction

Cancer is the second-leading cause of death globally and is also associated with a highly compromised quality of life [1]. Over the next two decades, the number of new cancer cases is expected to rise by approximately 50 % worldwide. Also, cancer treatment alone costs the world about US$1.2 trillion annually, which is nearly 2 % of the global gross domestic product in 2019 [2]. Even though recent cancer treatments have offered better life expectancy, such treatments are not entirely free of side effects or complications [3,4]. In addition, for those with long-term cancer and multiple comorbidities, the management of cancer symptoms, along with oral oncolytic and their toxicities, have increased the burden of complications on a cancer patient [4]. Such patients often face challenges with the development and management of other diseases, leading to multimorbidity, poor response to treatments, age-related changes, increased frailty, and potential premature mortality [5,6]. In the last two decades, greater emphasis has been given to easy availability of early detection programmes, better care

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coordination, preventive measures, and palliative care regimens, including the use of complementary and alternative medicine (CAM) for cancer patients, all of which can contribute significantly to improve their quality of life [5,7]. These methods have been considered strongly by patients across the globe for various illnesses without much evidence on their effectiveness and efficacy [8]. Ayurveda is one of the globally recognised complementary and alternative medicinal systems that originated and evolved in India and has been practised for thousands of years. It is best defined as the "science of life" for the improvement of holistic health with personalised treatments based on the "prakriti" (nature) of the body. Several Ayurvedic medications have been used to treat and manage a variety of human ailments. Recently, the use of Ayurvedic formulations in cancer management has gained attention from the scientific community across the world [9–11]. However, most of the literature has documented the effects of either traditional Chinese medicine (TCM) [12] or has been limited to establishing evidence on the use of single herbs or components such as curcumin or ashwagandha for cancer-related outcomes [13,14]. Moreso, the role of polyherbal formulations is much more convincing as compared to single herbs in terms of efficacy and effectiveness [15–17]. However, there are no documented studies available on the role of Ayurvedic polyherbal formulations in cancer treatments and improvement of quality of life of cancer patients. Therefore, it is imperative to investigate any study that is available on these formulations. One such ayurvedic polyherbal formulation is Maharishi Amrit Kalash, or "MAK.

1.1. Properties and benefits of MAK

MAK is a two-part polyherbal formulation (MAK-4 and MAK-5), based on the concept of "Brahma Rasayana" category of the rich texts of ancient Ayurveda system of medicine (Ayur = Life; Veda = Knowledge). A Rasayana (Rasa = essence, Ayana = going) is a potent rejuvenation therapy that helps bring overall balance to the physiology by maintaining nutrition at both macro and micro cellular levels [18]. It promotes health by replenishing the body's Rasa Dhatus (vital fluids), boosting the Ojas (vital force of life) and the immune system, and bringing equilibrium to the other Dhatus (tissues). MAK-4 is combination of thirty-eight herbs lyophilized in cow ghee [19] and MAK-5 composed of thirteen herbs and MAK-7 is modified MAK-4 without ghee, whole cane sugar, and honey in tablet form. The ingredients of MAK have been detailed in supplementary file Table S1. MAK has been used extensively for the past thirty years in improving overall health by improving immunity, reducing stress, delaying ageing, improving memory, and increasing the stamina [20–31]. These effects of MAK on various health factors have been established in different clinical and preclinical studies. As an Ayurvedic supplement, MAK has substantial research demonstrating exceptional effectiveness in the fields of anti-cancer and anti-chemotoxicity [26,32–40] as well as in the field of antioxidants [41–50], immunity [20–23,51–56], heart health [28–31, 57–60], ageing and vitality [24,25], maintenance of physiological homeostasis [61], and prevention of the development and propagation of disease [62]. It is a well-known fact that antioxidants play a direct and crucial role in the prevention of various other diseases like atherosclerosis, ocular disease, ageing and cancer [63]. Significant antioxidant properties of MAK have been described by Dwivedi et al. (2005) in a study that showed that aqueous and alcoholic extracts of MAK-7 are 60 and 166 times more potent than vitamin E in their antioxidant action when tested on rat liver microsomes [64]. Also, in a recent case series by Zanella et al. (2015), ORAC value for one dose (10 g) of MAK twice a day was found equivalent to that of 500 g of oranges, which peaks at about 9 h after its first intake [65]. In addition, MAK inhibits endothelial cell (EC) and soybean lipoxygenase (SLP)-induced LDL oxidation in a concentration dependent manner, much more than Vitamin C, Estradiol, and Estrone [66]. Niwa et al. (1991) and multiple other studies have identified MAK as an immunomodulator because of its suppressive effect on inflammatory mediators, especially reactive oxygen species [25,28, 55,56]. Other benefits of MAK have also been documented in a variety of observational studies: rehabilitative therapy for chronic head injury patients [67], depression and anxiety [68,69]. Studies with MAK as part of multimodality treatment have also shown positive effects on prevention of atherosclerosis [70], reducing the risk of juvenile drug and alcohol abuse [71], and symptom management of chronic diseases [72].

A possible reason behind the pharmacological action of MAK could be the synergistic effects of its biochemical ingredients. Previous studies have shown the presence of strong antioxidants like tannic acid, flavonoids, tocopherol, curcumin, ascorbate, carotenoids, polyphenols, alkaloids, tannins, flavonoids, steroids, and terpenoids in MAK [73–75]. Due to the synergistic effect of multiple herbs in MAK, its expected impact on chronic disease is relatively multi-fold as compared to single herb formulations [73]. Even though MAK has shown anti-neoplastic and anti-chemotoxicity effects on various types of cancers *in vitro*, *in vivo*, and in clinical settings [26,32–40], there is no single document synthesizing the extent of evidence on MAK use for such properties and the knowledge gaps on safety and efficacy of the compound. The data on use of MAK among cancer patients is scattered and needs to be reviewed for identifying a potential anti-neoplastic therapy and/or adjuvant therapy for reducing the burden of traditional treatments of cancer.

1.2. Scoping reviews

Scoping reviews are used to determine the scope or entire body of literature available on a given topic to provide an overview (broad or detailed) and/or a clear indication of the existing volume of literature [76–78]. The purpose of scoping reviews is inherently different from that of systematic reviews, although they may serve as a foundation for conducting systematic reviews. Systematic reviews are designed to answer a specific question, including systematic appraisal of studies, and delivering meaningful conclusions to end users [79], whereas scoping reviews are particularly designed to identify all available evidence on a given topic, clarify key concepts/definitions in the literature, and identify and analyze existing knowledge gaps [80]. The current scoping review was conducted to examine the volume and type of literature available on the use of MAK for cancer and chemotoxicity, qualitatively assess the strength of such evidence, summarize the main findings, and provide a clear conclusion on the extent of research available on MAK as a base for conducting further research. Our specific research question was developed to answer the extent of available evidence on the effectiveness of MAK as an anti-neoplastic and chemoprotective agent.

2. Methods

The review was conducted in multiple steps: developing a research question, conducting a systematic review, selecting studies based on our inclusion and exclusion criteria, recording key findings of each study, qualitatively summarizing findings, and providing a conclusion on the extent of research evidence and the need for future research [81,82]. The systematic review process followed the guidelines of the PRISMA checklist extension for scoping reviews [82].

2.1. Eligibility criteria

All research studies, including *in vitro*, *in vivo*, and clinical studies (both observational and randomized controlled trials), focusing on MAK as the main therapy of use, were selected. Studies examining the role of MAK for its anti-cancer, anti-metastases, anti-carcinogenesis, and chemoprotective properties were chosen and finalized for analyses. MAK was defined as the use of any of the following: MAK-4/MAK-5/MAK-7, or a combination of MAK-4 (Nectar) and MAK-5 (Ambrosia) or MAK-7 (a tablet form of Nectar) and MAK-5 (Ambrosia). Full-text articles and abstracts from conference proceedings were included, whereas review articles, case reports and articles in languages other than English were not included in this review. Studies with no full texts were excluded. For

abstracts, the original authors were contacted for any additional reports, summaries, or raw data supporting the abstracts. Ongoing clinical trials are not included as part of the final data but have been discussed in the discussion section of the paper.

2.2. Search strategy

Databases such as PubMed, Google Scholar, EBSCO, the AYUSH research portal, DHARA online, Clinicaltrials.gov, and the Clinical Trials Registry-India (CTRI) using search terms such as "Maharishi Amrit Kalash" or "Amrit Kalash" or "Amrit" or "MAK-4/MAK-5/MAK-7″ or "M4/M5/M7" or "Amrit Nectar" or "Maharishi". The search terms and systematic review process were enhanced by multiple iterations of similar search terms. For the first set of literature searches, these terms were searched in full text, followed by limiting them to the title and abstract. No date restrictions were used. Additional studies were found using the reference lists of the selected articles. For the full text of some articles and grey literature, local libraries, and other sources of research databases, such as Maharishi University resources (Maharishi International University, Iowa), Maharishi Ayurveda related websites (http://maharishi-india.org/healthresearch.htm), original authors of studies, and the manufacturer of MAK, were contacted. For ongoing clinical trials, principal investigators were requested to submit a preliminary report, where possible. Detailed search terms have been mentioned in supplementary file Table S2.

2.3. Study selection

Two reviewers (RV and RS1) were responsible for searching, screening, and reviewing articles. Discrepancies, if any, were resolved by a third reviewer (RS2). Microsoft Excel was used to record all data for search hits and selected research studies. A bibliography of all articles pertaining to MAK use was created in Microsoft Word and those pertaining to cancer and chemotoxicity were manually identified. After the initial screening, inclusion and exclusion criteria were applied and selected studies with full texts or abstracts were selected. The full text of all selected articles was read in detail and themes were developed by using a coding scheme developed.

2.4. Data synthesis

The full text of all articles with MAK as the main source of therapy and cancer outcomes were picked manually. Studies presented as conference proceedings were analyzed separately. For all articles selected, a table with PICO principles (Table S31: Patient Population, Intervention, Comparator, and Outcomes) was prepared. Key themes on the properties of MAK were developed using frequency coding (qualitative analyses). However, the review provides an overall assessment of the quality of the studies included in it. After establishing inclusion and exclusion criteria, 20 studies with MAK as the main source of therapy and a cancer outcome were identified. Out of these, duplicate studies presented at conferences and converted to full-text papers (3), studies with the inclusion of MAK as part of a multiple comparison with other chemotherapeutic agents

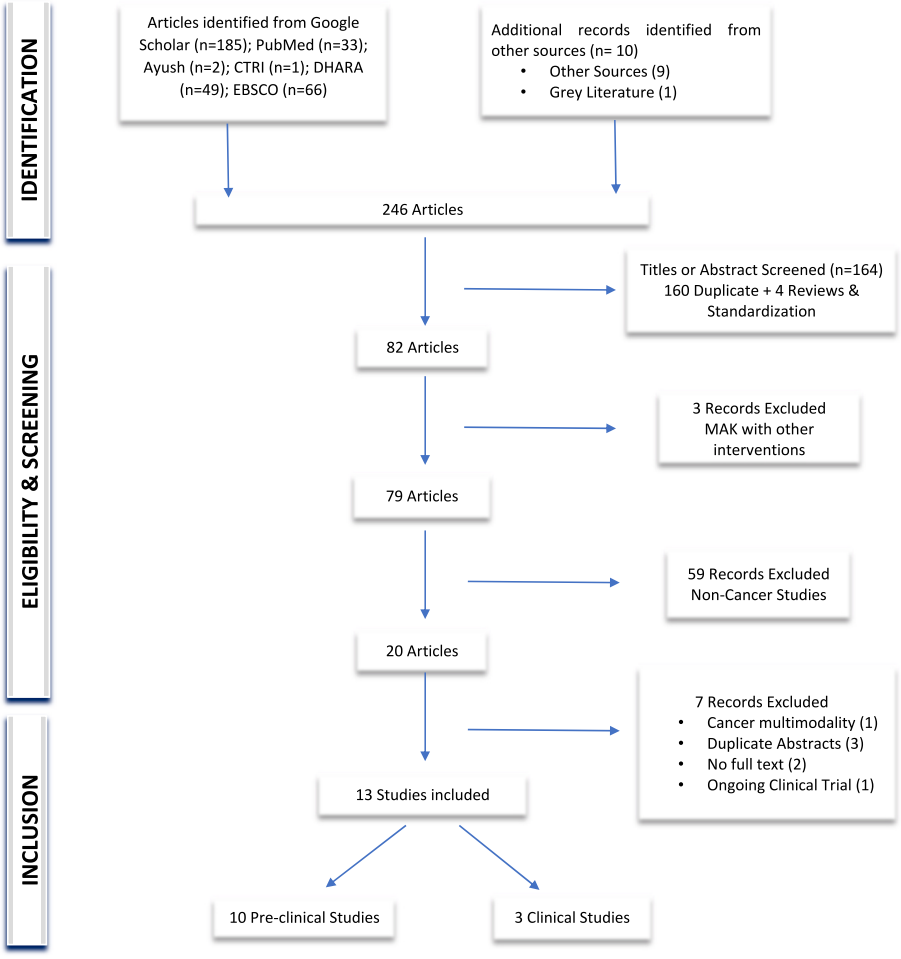

Fig. 1. PRISMA flow diagram for article inclusion process.

(1), studies with no full text (2), and studies at the clinical trial stage (1) were removed from the final review. The full text of 13 studies could be retrieved from various sources for the final review, and the data presented here is a synthesis of those 13 studies (Fig. 1).

3. Results

In total, 13 research studies of varying designs were finalized for final review, of which 10 were conducted at the preclinical level and 3 at the clinical level. Out of the 13 studies, 4 studies were conducted on MAK-4, 3 studies on MAK-5, and 6 studies on MAK-4 and MAK-5 together. All studies conducted on MAK and cancer related outcomes ranged from 1988 to 2008 and were primarily conducted in the geographic regions of the US and India.

3.1. Preclinical studies

Full texts of 10 preclinical studies on MAK and its effects on cancer and chemotoxicity were retrieved. Out of which, 4 studies were *in vitro*, 5 studies were *in-vivo*, and 1 study was a combination of both *in vitro* and *in vivo* research. The scope of these studies includes determining the effectiveness of MAK on the initiation of neoplastic transformation of cancer cells [83], carcinogenesis inhibition [32,39], inhibition or reduction of metastases [38], retardation of cancer growth [39,40], induction of morphological and biochemical differentiation of cancer cells [37,84], and reduction in chemotoxicity [85]. Arnold et al. (1991) showed that MAK-4 and MAK-5 inhibited neoplastic transformation by inhibiting the morphological transformation of rat tracheal epithelial cells by 27 % and 53 %, respectively [86]. In another study on inhibition of cancer growth, ethanol extract of MAK-5 inhibited the growth of murine B-16 cells after only 24 h of treatment, whereas both MAK-4 and MAK-5 inhibited the growth of human melanoma cells [38]. In two separate animal studies, Sharma et al. [33,83] showed that MAK-4 and MAK-5 supplementation reduces DMBA-induced mammary tumour incidence and multiplicity, with a possible mechanism of action of blocking estrogen and progesterone receptors.

Two *in vitro* studies by Prasad et al. [37,84] showed the effect of MAK in inducing the morphological and biochemical differentiation of murine neuroblastoma cells (MAK-5) and human melanoma cells (MAK-4 and MAK-5) respectively. Rodella et al. [87] confirmed these findings by showing the synergistic effect of MAK-5 on nerve growth factor (NGF)-induced morphological differentiation of PC12 cells, possibly by activating a common cellular pathway with NGF and simultaneously a proliferating and differentiating pattern. An animal study by Sharma et al. [88] showed the protective effect of MAK-4 against cisplatin induced toxicities, where it reversed the effect of cisplatin on the glutathione (GSH) and glutathione-S-transferase (GST) activities in rat liver and kidney. Dwivedi et al. [40] observed that the addition of MAK-4 to the rat diet inhibited the development of 7,12-dimethylbenz (*a*)anthracene (DMBA)-induced mammary tumours in rats. Penza et al. [32] significantly inhibited RAS oncogene-induced cell transformation in the Rat 6 cell line. Also, in tumour-positive mice, liver nodules were significantly lesser in the MAK-4 (35 %), MAK-5 (27 %), and MAK4+5 (46 %) supplemented groups as compared to the control group. It was seen that MAK-4 and MAK4+5 treated groups had a higher ORAC ($p < 0.05$) value and higher activities of glutathione peroxidase (GPx), glutathione-S-transferase (GST), NADPH and quinone reductase (QR) as compared to controls. Livers of MAK-fed mice showed a time dependent rise in expression of the connexin (CX32) protein. Effect of MAK on metastases was shown by Patel et al. (1990, 1992) [38,39], where MAK-4 was found to reduce the number and size of Lewis Lung Carcinoma (LLC) metastatic nodules in female mice. These interesting results from these studies provide a strong basis for further investigation to look at their effect in clinical settings and their mode of action.

3.2. Clinical studies

All three MAK clinical trials investigated the effect of adjuvant MAK therapy on cancer treatment-related outcomes. Two of the clinical trials focused on breast cancer patients, and one clinical trial focused on all types of cancer and did not have any randomized allocation [29–31] of patients. Misra et al. [34] conducted a prospective two-armed study on 62 patients (nMAK = 38 and ncontrol = 24) with a variety of cancers, including non-Hodgkin's lymphoma, ovarian cancer, breast cancer, and others, who were undergoing chemotherapy. The MAK group showed improvement in symptoms like vomiting (n = 42), diarrhoea (n = 44), sleep (n = 35), weight (n = 24), and an overall feeling of well-being (n = 40). It also reduced the lipid peroxide significantly ($p = 0.02$) in 3 months of MAK intake with chemotherapy. Also, there was a reduction in the hematologic toxicity like leukopenia and thrombocytopenia in the MAK patients. Another breast cancer clinical trial conducted by Samaiya et al. [35] provided additional evidence in favour of the findings. In an open randomized controlled experiment done at AIIMS, New Delhi, 129 breast cancer patients (MAK: 61 patients, Control: 68 patients) were studied to determine the effectiveness of MAK in minimising chemotoxicity. The MAK group was shown to have a lower relative risk (RR) and cumulative incidence (CI) of a side effect than the control group. After the fourth cycle, MAK patients showed statistically significant improvements in the Karnofsky Performance Scale (KPS) (95 % confidence intervals, i.e., c.i. 1.06–2.45, the relative risk, or RR, = 1.64, $p = 0.02$), anorexia (95 % c.i. 14.1–6.6, the prevented fraction (PF) = 42 %, with RR = 0.5, $p = 0.004$), vomiting (95 % c.i. 0.25–0.8, PF = 54 %, RR = 0.46, $p = 0.008$), and stomatitis (95 % c.i. 0.2–0.8, PF = 55 %, RR = 0.40, $p = 0.01$) after the 4th cycle) in MAK patients. In addition, patients in the MAK group were able to maintain their body weight throughout the study period as compared to the control group, which experienced an average of 1.12 kg of weight loss. No significant difference was observed for the tumour response in both groups. Another randomized controlled trial, placebo-controlled study by Saxena et al. [36] on 214 breast cancer patients randomized to either MAK (n = 102) or control groups (n = 112) conducted at AIIMS, New Delhi, showed the role of MAK in relieving the symptoms caused by the side effects of chemotherapy. A better appetite with RR at end of 5th cycle = 0.39, 95 % CI = 0.20–0.78, $p = 0.005$, PF = 60.6, 95 % CI = 22.1–80.1), for anorexia, and reduced vomiting (95 % c.i 9.1–55.1, PF = 36.1 %, $p = 0.01$) were seen in MAK patients. A greater proportion of patients in the control group reported lower KPS after each cycle. Most significant difference was seen after 5th chemotherapy cycle with (95 confidence interval 22.1–80.1, PF = 60.6 %, RR 0.39 $p = 0.005$. (KPS≤70 %; at 95 % c.i., 0.20–0.78, PF = 60.69 %, RR = 0.39, $p = 0.005$), and better maintenance of weight throughout the study. No statistically significant difference was observed between the two groups for the effect on stomatitis, alopecia, diarrhoea, and leucopenia. The studies showed that MAK is an excellent adjuvant in cancer treatment to minimize the side effects of chemotoxicity.

3.3. Toxicity: MAK-4 and MAK-5 were found to be slightly toxic in the Rat 6 cell line in one *in vitro* study [26], but not in other cell lines [37,87,89]. No other studies reported any toxic effects of MAK, which was well tolerated across various cell lines, animals, and humans in a range of multiple dosages (10–20 g per day) [57,59,61,87].

3.3. Details of excluded studies

All the relevant studies on MAK and cancer outcomes were screened for specificity out of which few studies were excluded because of either a lack of full text [83] or a non-focused approach on MAK as an independent therapy [84]. In this non focused research by Arnold et al. (1995) chemo preventive effects of 99 different natural and synthetic compounds was evaluated the using a rat tracheal epithelial cell culture

assay, where MAK-4 and MAK-5 were found to cause 76 % and 64 % inhibition, respectively, as compared to ferulic acid and curcumin with 100 % and 91 % inhibition, respectively.

4. Discussion

In India alone, the estimated cancer mortality rate is expected to increase to 0.70 million by the year 2026 and greater stress is given to reduce risk factors and improve the quality of life of patients with cancer [91]. The present scoping review is conducted to highlight a possible therapy for reducing the risk of cancer as well as improving the well-being of patients undergoing chemotherapy. In the current review, we synthesized data from studies that have analyzed MAK as a potential anti-neoplastic agent and chemo protectant. We found that MAK's effectiveness as an anti-cancer agent is primarily due to its participation in tumour growth inhibition, carcinogenesis inhibition, induction of differentiation of cancer cells, and metastases reduction. MAK was also found to be consistent in alleviating side effects associated with chemotherapy, mainly anorexia, vomiting, loss of appetite, body weight and an improvement in the overall well-being of cancer patients. An ongoing clinical trial at AIIMS, New Delhi, is comparing the effectiveness of MAK vs. no MAK as an adjunct therapy for breast cancer patients receiving neoadjuvant chemotherapy [92]. Preliminary rough findings among 102 patients have indicated the MAK group reported better clinical outcomes but no significant difference in tumour regression as compared to the control. Final findings will be reported once a full sample size is recruited. Authors of the studies on MAK have also highlighted its mechanism of action as an anti-neoplastic agent primarily through its protection against oxidative damage [33,36,89], enhanced immune functioning [23], and participation in carcinogenic events through multiple pathways [33,37,84,87,90]. MAK's role in reducing chemotoxicity was majorly linked to a reduction in free radical and reactive oxygen species (ROS)-related cell injury. MAK was proposed to enhance superoxide scavenging abilities [48], reduce lipid peroxides [65], enhancement of GSH and GST activity for protection and detoxification [72] to reduce the side effects of chemotoxicity. Other proposed mechanisms of action for MAK are discussed as follows:

4.1 Tumour growth inhibition: Sharma et al. [33] proposed that the anti-neoplastic action of MAK-4 causes regression of mammary tumours by maturation of tumours with differentiation towards benign morphology and associated fibrosis. The possible pathways are a reduction in beta-endorphins (stress-associated hormones) and an increase in already reduced CNS Met-Enkaphlins (opioid peptides known to influence carcinogenic events) in MAK-4 treated rats. In another study on DMBA-induced mammary tumours, the role of MAK-5 in providing protection and tumour regression during the promotion phase (MAK-5 supplementation one week after induction of the tumour) was linked to blockage of estrogen and progesterone receptors.

4.2 Cellular differentiation: Prasad et al. [37,84] supported the hypotheses that MAK-4 and MAK-5 are anticancer agents at both the growth inhibition and differentiation levels. But these effects were relative to the type of cancer cells (human or murine melanoma), the dose of these agents, and the presence of serum. A possible mechanism of action was an increased intracellular level of cyclic AMP (involved in the differentiation of neuroblastoma cells) after three days of MAK-5 treatment. The study also showed that exposure of neuroblastoma cells to MAK-5 in serum free medium for 24 h or in serum for 3 days is sufficient to alter the genetic expressions responsible for maintaining the transformed phenotype of these cells in culture, which are later expressed as a differentiated phenotype. Rodella et al. [87] highlighted a synergistic effect of MAK-5 treatment on nerve growth factor (NGF)-mediated neuronal differentiation in PC12 cells, due to the presence of both differentiation and proliferating agents in MAK-5, simultaneously causing a change in the expression of Tyrosine Hydroxylase (TH).

4.3 Metastases reduction: Patel et al. [38] hypothesised that the reduction in LLC metastases in mice on MAK-4 supplemented diet was possibly due to increased lymphocytic infiltration, suggesting possible immune mechanisms at work. In addition, antioxidant action and free radical scavenging could also play a role in reducing the size and number of metastatic nodules in mice.

4.4 Carcinogenesis inhibition: Penza et al. [32] highlighted the strong antioxidant role MAK-4 and MAK-5 for preventing carcinogenesis both *in vitro* and *in vivo* settings. MAK was shown to inhibit RAS oncogene-induced cell transformation by providing a strong line of antioxidant defence, as shown by continuously increasing oxygen radical absorbance capacity (ORAC) values, upregulation of activity of liver enzymes such as GPx, GST, and QR (involved in causal mechanisms in protection from carcinogens), and higher connexin Cx32 levels (MAK induces up-regulation of Cx expressions possibly by enhancing gap junctional communication in the liver of CH3HeJ mice like other antioxidants) in mice fed with MAK as compared to control mice.

4.1. Limitations

The current scoping review was limited in many aspects. Studies were not excluded based on their methodological quality to provide comprehensive and broad evidence on the actions of MAK, an area that has not been delved into before. Most of the studies were conducted at the preclinical level, with no substantial evidence from clinical settings. Therefore, results from these studies should be interpreted cautiously. Data on the anti-neoplastic actions of MAK from pre-clinical studies was only examined in two of the three clinical trials conducted on MAK and cancer outcomes [34,35]. Neither of the two studies showed a significant difference between the MAK and control groups in their tumour regression after undergoing chemotherapy. Therefore, a greater number of human studies with larger sample sizes are needed to confirm the anti-neoplastic effects of MAK. After our final screening, the number of studies presented here, even though significant, is very low. In addition, since these studies were conducted in the early 1990's, more recent data is needed to confirm our findings. Nonetheless, the evidence on MAK available in this review can be used as a platform to delve deeper into an emerging need in cancer research for newer treatment and prevention approaches. We used a specialist in herbs (Dr. Richa Shrivastava) to assess the strength of our studies and interpret the results from these studies. We could not conduct a quantitative appraisal of the quality of these studies and their findings, which is also out of scope for this review.

5. Conclusion

1) MAK has some strength of evidence for its anti-neoplastic effect from pre-clinical trials, which is sufficient to explore in human trials; 2) MAK has medium-strong evidence for its chemoprotective actions consistently shown in three different clinical trials, placing MAK as a strong potential therapy to alleviate symptoms of chemotherapy, and improve the overall well-being of patients with cancer. MAK could be an excellent Ayurvedic approach for helping patients with cancer, and it could be well-placed as a mainstream therapy for its effects on tumour growth once these have been well explored in the future.

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Author contribution

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

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaim.2023.100866.

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