



Research Journal of Pharmaceutical, Biological and Chemical Sciences

An Advance Innovation Of Dosage Form Of Traditional Medicines In Various Diseases.

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ABSTRACT

Nature has been a source of medicinal agents for more than thousands of years and herbal therapy predominates in traditional systems of medicine as well as in alternative medicine practiced in various cultures such as Indian system of medicine, Chinese Traditional Medicine, Unani classical literature. The present review deals with various polyherbal formulations used by different countries of the world. Information on traditional herbal formulations was documented in the form of research and review articles in various journals. The aim of this review is to summarize the different types of herbs used for the preparation of polyherbal formulations, their therapeutic potentials including clinical and preclinical results along with their safety and efficacy. This review will facilitate to gain all about the past scientific research and the necessary information about the enormous pharmacological activities of polyherbal formulations which will insist the young researchers for future research to protect human beings from various types of diseases and may serves as a natural gold for the promotion of mankind.

Keywords: Withania somnifera, Polyherbal, HK-07, Chooranam, Rumalaya Forte, Thapring.

<https://doi.org/10.33887/rjpbcs/2022.13.1.10>

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INTRODUCTION

Herbal products are of interest to many patients and health care practitioners because more than 70% of World's population is rely on herbal medicines for part of their primary health care system. In different regions and cultures, herbal products are used as single herb, combination of herbs, or combination of herb(s) and drug(s). Due to several side effects of allopathic medicine, in recent years there has been an increase in the use of herbal medicine by the majority of population throughout the World. Polyherbal formulations with various active principles and properties have been used from ancient days to treat a wide range of human diseases. Polyherbal formulations are collection of therapeutic entities that are formulated and prepared on the basis of the healing properties of individual ingredients with respect to the condition of sickness. Such herbal constituents with diverse pharmacological activities principally work together in a dynamic way to produce maximum therapeutic benefits with minimum side effects. Nevertheless, these traditional medicinal preparations gradually lost their popularity and foothold among people due to the fast therapeutic action of allopathic system of medicine. In recent years however, renewed interest has grown on traditional herbal remedies because of many side effects observed by using synthetic drugs in allopathic medicine. At the same time, WHO also recommends further research on traditional system of medicine [1].

Currently, polyherbal formulations are employed for the treatment of various types of diseases, such as respiratory diseases, cancer, acquired immunodeficiency syndrome (AIDS), diabetes and ulcer in order to achieve enhanced therapeutic effects. In the present review we have included different types of polyherbal formulations used for the treatment of respiratory diseases along with other activities like immunomodulatory effects, anti-inflammatory, antipyretic, anti-microbial, antioxidant, antidepressant, CNS depressant, diuretic, myocardial infarction, anti-cancer, anti-HIV and toxicity study also.

Advance Innovation Of Traditional Medicines Having Anticancer Activity

Lung Cancer

In vitro studies have shown that root extracts of WS exhibited cytotoxic properties against lung, colon, central nervous system, and breast cancer cell lines [2]. WS Dunal has been shown to possess tumor preventing activity against urethane induced lung- adenomas in adult male albino mice by inducing a state of nonspecific increased in resistance (Adaptogen) and immunostimulant properties [3]. Pharmacokinetic studies in mice revealed that WFA reaches peak concentrations up to 2 μ M in plasma with a half-life of 1.36 h following a single 4 mg/kg dose. In a breast cancer metastasis mouse model, WFA showed dose-dependent inhibition of metastatic lung nodules and induced vimentin ser 56 phosphorylation, with minimal toxicity to lung tissue [4]. Recent studies showed that ashwagandha extract inhibited the growth of human breast, lung, and colon cancer cell lines in the laboratory. This inhibition was comparable to that achieved with the common cancer chemotherapy drug doxorubicin (Caelyx®, Myocet®). In fact, researchers reported that withaferin A, a specific compound extracted from ashwagandha, was more effective than doxorubicin in inhibiting breast and colon cancer cell growth [2, 5]. In another study, the combination of paclitaxel with *W.somnifera* could effectively treat the benzo(a)pyrene-induced lung cancer in mice by offering protection from reactive oxygen species damage and also by suppressing cell proliferation [6]. In another study and Based on the data, the carcinogen as well as the paclitaxel, affects the immune system, the deleterious effects on the immune system is more reversible and more controllable by *W. somnifera* (L.) Dunal. These results show the immunomodulatory activity of *W. somnifera* (L.) Dunal extract, which is a known immunomodulator in indigenous medicine. [WS has been found to be beneficial in lung cancer [6].

Prostate cancer

The study conducted to evaluate in vitro cytotoxicity in 50% ethanol extract of root, stem and leaves of WS against five human cancer cell lines of four different tissues i.e. PC-3, DU-145 (prostrate), HCT-15 (colon), A-549 (lung) and IMR- 32 (neuroblastoma). Revealed that root, stem and leaves extracts showed cytotoxicity activity against ranging 0-98% depending on the cell lines but maximum activity was found in 50% ethanol extract of leaves of WS. Further, ethanol extract of leaves obtained from treatments T2, T3, T4 and T5 showed strong activity against PC-3 and HCT-15 with 80- 98% growth inhibition, while the 50% ethanol extract of

leaves from T1 treatment showed a minimum of 39% and T3 treatment showed a maximum of 98% growth inhibition against HCT-15 [7].

Pancreatic Cancer

The study conducted to investigate the efficacy and the mechanism of Hsp90 inhibition of Withaferin A (WA), a steroidal lactone occurring in WS, in pancreatic cancer in vitro and in vivo revealed that Withaferin A acts as a potent antiproliferative activity against pancreatic cancer cells in vitro (with IC₅₀ of 1.24, 2.93 and 2.78 μ) in pancreatic cancer cell lines Panc-1, MiaPaCa2 and BxPc3, respectively. The results of the study demonstrate that Withaferin A binds Hsp90, inhibits Hsp90 chaperone activity through an ATP-independent mechanism, results in Hsp90 client protein degradation, and exhibits in vivo anticancer activity against pancreatic cancer [8].

Advance Innovation Of Traditional Medicines Having Antiasthmic Activity

A polyherbal formulation (PHE) was prepared by using ethanolic extract of *Adhatoda vasica*, *Clerodendrum serratum*, *Curcuma longa*, *Solanum xanthocarpum* and *Piper longum* in the proportion of 40%, 30%, 10%, 10% and 10%, respectively by Gohil et al. The mast cell stabilizing and anti-anaphylactic property of this PHE was investigated against compound 48/80-induced mast cell degranulation as well as triple antigen-induced anaphylaxis in rats. The polyherbal formulation produced significant reduction in the mortality of rats subjected to triple antigen-induced anaphylactic shock. It also depicted marked protection of rat mesenteric mast cells from disruption by compound 48/80 in dose dependant manner. Their study suggested anti-anaphylactic and mast cell stabilizing properties of the polyherbal formulation [9].

HK-07 is a polyherbal formulation containing mainly the extracts of *Curcuma longa*, *Zingiber officinale*, *Piper longum*, *Embllica officinalis*, *Terminalia bellerica*, *Ocimum sanctum*, *Adhatoda vasica* and *Cyperus rotundus* was prepared by Gopumadhavan et al. The antianaphylactic activity of HK-07 was investigated in rats using the active anaphylaxis model. The effect on mast cell stabilization was performed by ex-vivo challenge of antigen in sensitized rat intestinal mesenteries. Antihistaminic activity was studied in guinea pigs using histamine-induced bronchospasm where preconvulsive dyspnea was used as an end point following exposure to histamine aerosol. Dose response studies of HK-07 were conducted at 125, 250, and 500 mg/kg, p.o. in anaphylactic shock-induced bronchospasm in rats. The optimal dose level was used for the remaining experimental models. Treatment with HK-07 at different test concentrations showed significant reduction in signs and severity of symptoms ($P < 0.05$), onset ($P < 0.001$) and mortality rate ($P < 0.05$) following anaphylactic shock-induced bronchospasm. HK-07 also significantly reduced the serum IgE levels ($P < 0.001$) in animals compared to untreated controls. Treatment of sensitized animals with HK-07 at 500 mg/kg, p.o. for 2 weeks resulted in a significant reduction in the number of disrupted mast cells ($P < 0.001$) when challenged with an antigen (horse serum). HK-07 significantly prolonged the latent period of convulsion ($P < 0.008$) as compared to control following exposure of guinea pigs to histamine aerosol [10].

Bharangyadi is a polyherbal compound having *Clerodendrum serratum*, *Hedychium spicatum* and *Inula racemosa* as an ingredient herbs. Evaluation of the anti-asthmatic activity of Bharangyadi through various in-vitro and in-vivo experimental models was carried out by Divya Kajaria et al. The results demonstrate that Bharangyadi has potent histamine antagonism property with significant mast cell stabilizing and spasmolytic activity in the experimental animals. Ethanolic extract of Bharangyadi at the doses 500 and 1000 μ g/ml protected from compound 48/80-evoked degranulation in dose dependent manner. Pre-treatment with Bharangyadi extract showed 80% and 86% protection from histamine induced bronchoconstriction in guinea pigs with 27.8% and 36.1% increase in preconvulsion time (equal to standard drug). Screening of Histamine antagonism activity on guinea pig ileum showed that Bharangyadi reduces the smooth muscle contraction in dose dependent manner. Increasing concentration of Bharangyadi extract with maximum dose of histamine (1.6 μ g) showed maximum inhibition at the dose of 50 mg (99.78%) [11].

A combination of three traditional Chinese medicinal herbs was used to prepare an anti-asthma polyherbal formulation known as ASHMITM by Bolleddula et al. They designed a study to determine if the anti-inflammatory effects of individual herbal constituents of ASHMITM exhibited synergy. Effects of ASHMI and its components aqueous extracts of *Ganoderma lucidum*, *Sophora flavescens* and *Glycyrrhiza*

uralensis, on Th2 cytokine secretion by murine memory Th2 cells (D10.G4.1) and eotaxin-1 secretion by human lung fibroblast (HLF-1) cells were determined by measuring levels in culture supernatants by enzyme linked immunosorbent assay. Potential synergistic effects were determined by computing interaction indices from concentration-effect curve parameters. Individual herbal extracts and ASHMI (the combination of individual extracts) inhibited production of interleukin (IL)-4 and IL-5 by murine memory Th2 cells and eotaxin-1 production by HLF-1 cells. Their study showed that ASHMI is significantly more potent than any of its constituent herbs in direct suppression of IL-4 and IL-5 production by Th2 cells (no overlap in the 95% confidence intervals for IC₂₅ or IC₅₀) and this is due to synergism among the ASHMI constituents. Thus ASHMI has demonstrated efficacy in both mouse models of allergic asthma and a double-blind placebo-controlled clinical trial in patients with asthma [12].

A polyherbal formula containing *Picrorrhiza kurroa*, *Picrorrhiza kurroa* and *Zingiber officinale* was prepared and screened against asthma by Thomas et al. A crossover, randomized control study with this combined formula and a standardized extract of *Ginkgo biloba* were investigated on therapy-refractory asthmatic patients. No significant improvements in asthma symptoms, pulmonary function test (PFT) and quality of life could be seen [13].

A polyherbal formulation contains different types of herbs such as *Astragalus mongholius*, *Cordyceps sinensis*, *Radix stemonae*, *Bulbus fritillariae* and *Radix scutellariae* was prepared by Wong et al. A randomized, double-blind, placebo-controlled trial of this herbal therapy for children with asthma performed in pediatric asthma patients for six months. The results of the study showed no improvement in lung function tests and other biometrical parameters [14].

Thuthuvalayathy Chooranam is a polyherbal formulation contains *Solanum trilobatum*, *Aristolochia indica*, *Alpinia officinarum*, *Nigella sativa*, *Madhuca lonifolia*, *Zingiber officinale*, *Piper nigrum*, *Piper longum*, *Terminalia chebula*, *Ferula asafetida* and *Piper longum*. Evaluation of safety of the Thuthuvalayathy Chooranam through acute and sub acute toxicity study was carried out by Nalini et al. In an acute toxicity study the drug was administered orally at a dose 2700 mg/kg p.o. and the animals were observed for any toxic symptoms up to 72 hours. The results indicated that there were no toxic symptoms up to the dose level of 2700 mg/kg p.o. In case of sub acute toxicity study Thuthuvalayathy Chooranam was tested at a dose ranging from 270 mg/kg, 1,350 mg/kg and 2700 mg/kg p.o. once daily for 30 days. The animals were sacrificed on 31st day. The liver, heart, lung, stomach and kidney were processed for histopathological study. The result of the sub acute toxicity study did not show evidence of any changes in body weight, food and water intake when compared with the control animals. The study revealed that Thuthuvalayathy chooranam formulation at different doses of 270, 1350, 2700 mg/kg did not show toxic effects in the animal's tissues and it was safe when administered to bronchial asthma patients [15].

An herbal compound formulation Pentapala-04 prepared from five medicinal plants namely, *Adhatoda vasica*, *Ocimum sanctum*, *Coleus aromaticus*, *Glycyrrhiza glabra* and *Alpiania galangal*. The effect of "Pentapala-04" on ova albumin and aluminium hydroxide induced lung damage in albino wistar rats was investigated. The rats were divided into three groups of four animals each. Group I, II and III serves as control, toxic and post treatment group respectively. The results showed that there was increased level of lipid peroxidation and decreased level of antioxidants in toxic group animals. But the levels of antioxidant enzymes were restored in post treated groups of animals, which might be due to the ability of Pentapala-04 to scavenge the reactive oxygen species. Thus they demonstrated that 'pentapala-04' prevents ova albumin and aluminum hydroxide induced oxidative stress, lung injury and inflammatory changes and can be used as an antiasthmatic drug.

Advance Innovation Of Traditional Medicine Having Anti-Hiv Activity

In a prospective, single-site, open-label, non-randomized, controlled, pilot trial, was carried out to evaluate an Indian polyherbal formulation (PHF) for its safety and efficacy in treating subjects with HIV-AIDS. A total of 32 and 31 subjects were enrolled under the PHF and highly active antiretroviral treatment (HAART) arms, respectively, and followed up for a period of 24 months. Plasma viral RNA, CD4 cell count and blood chemistry were monitored at 3-month intervals. Following mid-term safety evaluation, 12 subjects from the PHF arm were shifted to HAART and were followed separately as PHF-to-HAART arm, for the rest of the period. In the PHF arm, at 1 month, a significant increase in CD4 cell count and a concomitant decrease in viral load were seen. The PHF appears to have provided protection by delaying the kinetics of CD4 cell reduction [16].

Advance Innovation Of Traditional Medicine Used In Myocardial Infection

Abana is an Indian Ayurvedic herbomineral preparation of selected ingredients, which provides significant protection against ischaemia and hypertension. Its most important plant ingredients are Terminalia arjuna, Withania somnifera, Terminalia chebula, Phyllanthus emblica, Nardostachys jatamansi, Tinospora cordifolia, Glycyrrhiza glabra, Zingiber officinale and Nepeta hindostana etc. To find out the possible role of lipid peroxidation and glutathione in the pathogenesis of myocardial infarction and its protective role a study was conducted by Sheela et al. The effect of Abana pretreatment (75 mg/100 g) for a period of 60 days on isoproterenol (20 mg/100 g s.c. twice at an interval of 24 hrs) induced lipid peroxidation was studied in rats. Marker enzymes levels such as creatinine kinase, lactate dehydrogenase, alanine transaminase and aspartate transaminase were assessed in serum and heart homogenate. Glutathione content and lipid peroxide levels were also estimated. In isoproterenol administered rats, a significant decrease was observed in the levels of marker enzymes in the heart with a corresponding increase in their levels in serum. Lipid peroxide level measured in terms of "TBA reactants" increased significantly in serum and heart. Abana pretreatment offers significant protection to myocardium against the damage caused by isoproterenol induced lipid peroxidation [17].

Advance Innovation Of Traditional Medicine Having Cns Depressant Activity

Bramhi Ghrita, a polyherbal formulation containing Bacopa monneri, Evolvulus alsinoids, Acorus calamus, Saussurea lappa and cow's ghee. The effect of Bramhi Ghrita on motor coordination, behavior, sleep, convulsions, locomotion and analgesia was evaluated in mice using standard procedures by Achliya et al. The formulation exhibited reduced alertness, spontaneous locomotor activity and reactivity. It also antagonized the behavioral effects of d-amphetamine, potentiated the pentobarbitone induced sleep and increased the pain threshold. Bramhi Ghrita protected mice from maximum electroshock and pentylene tetrazole-induced convulsions. Bramhi Ghrita also showed antinociceptive action by tail flick method. Bramhi Ghrita inhibited MES and PTZ-induced convulsions in a dose-dependent manner. The study showed that Bramhi Ghrita was CNS depressant with anticonvulsant activities [18, 19].

CONCLUSION

Traditional system of medicine is one of the age-old practices and humans have postulated and ultimately established this system, in particular, the usage of traditional medicinal plants through empirical observation and by trial and error experiment. Even in the era of modern computational pharmacology approach, traditional medicinal plants serve as an important source and as a tool to treat various ailments in the developing countries. Currently, the world's most efficacious potent antimalarials such as chloroquine and artemisinin are the gifts of our precious traditional knowledge and custom of traditional medicinal plants. The recent success of drug development from medicinal plants inspires and encourages many researchers to investigate and validate the uses of traditional medicinal plants. However, there are many thorny issues and daunting challenges that need to be addressed effectively and immediately for the promotion of traditional medicinal plants. The collaborative efforts of ethnobotanists, anthropologists, pharmacists, and physicians could be a workable strategy to evaluate and validate the usage custom of traditional medicinal plants with the existing modern scientific methods and innovative techniques.

From our personal observation, being born and brought up in developing countries like India and Ethiopia, especially from the rural underprivileged section of the society, we have experienced that the sick primarily approach the proximate traditional healer who is the primary health care provider in that area. Subsequently, they may travel to the adjacent modern (allopathy) health facilities if they do not get completely cured by the former. In true sense, our traditional knowledge on medicinal plants plays a major role, especially in developing countries, and helps the rural poor to lead a healthier and disease-free life. Based on the existing data for the betterment of traditional medicinal plants practice and future prospects, the present review makes the following recommendations:

Recommendations

- In developing countries, a sizable fraction of the rural poor still depends on traditional herbal medicine; however, the efficiency and the intrinsic compounding factors are still unknown and

imprecise, which needs to be scientifically validated by conducting more detailed antimicrobial assays.

- Many believe that phytotherapeutic agents are quite safe; nevertheless, a few of them might have intrinsic toxicity too. There is a possibility of contamination or adulteration, and so these should be administered with great care and under the supervision of herbalist. Human safety must be determined by conducting standardized scientific clinical trials.
- In several instances, the administered herbal medicinal products' dosage is unknown or imprecise, which may lead to severe adverse side effects. Therefore, the desirable and appropriate dosage level must be determined by conducting more scientific experiments.
- Education programs such as short courses on modern traditional medicine or exposure to the subject in the undergraduate curriculum will be of benefit and will awareness among health care practitioners.
- Special herbal system of medicinal units should be established within the premises of the modern health facilities, which would offer the opportunity to the patients to acquire traditional medicine, based on their personal interest.
- Worldwide, conservation of traditional medicinal plants is a matter of grave concern. The well-known traditional *Materia Medica* should be protected and preserved by employing various projects to realize the plant conservation for our future need.

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