INT. J. BIOL. BIOTECH., 20 (4): 621-627, 2023.

ACUTE ORAL TOXICITY AND PRECLINICAL EFFICACY STUDY OF POLYHERBAL MULTIVITAMIN SUPPLEMENT

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ABSTRACT

Poly-herbal multivitamin supplement prepared by Real Herbal Laboratories Pakistan is a mixture of different medicinal plants with honey. Acute oral toxicity and efficacy studies of this poly-herbal multivitamin supplement were conducted in albino rats and rabbits respectively to assess its any toxicological/nutritional effects on general behavior, body weight, biochemical and hematological parameters. Acute oral toxicity study was carried out by adopting the OECD - 423 Guidelines. The poly-herbal product was administered orally at 300, 2000 and 5000mg/kg dose. All animals were kept under observation for 1, 2, 4 , 8 hours to monitor the signs of illness or mortality after oral administration of sample, and twice daily thereafter for 14 days. During the study, all rats were remained alive with normal appearance and showed increase in body weight. No gross lesions were observed in vital organs during autopsy. Biochemical and hematological analysis of 30days efficacy study in rabbits showed remarkable improvement in body weight and health condition of test group. There was an increase in hemoglobin level of test group animals as compared to the control group which were fed with vehicle only. White blood cells and Red blood cells count indicated that drug didn't create any adverse reaction in blood parameters. In longterm use of this poly-herbal supplement no signs of toxicity were found.

Key words: Acute oral Toxicity, multivitamin supplement. Efficacy study, Hematological analysis, Biochemical studies

INTRODUCTION

Plants have significant importance in the field of medicine and healthcare. They are rich with bioactive compounds and essential nutrients that can be utilized for therapeutic purposes, contributing to the well-being of individuals. The utilization of indigenous plant products for remedial, ethno-medicinal, and nutritional purposes has captured the attention of scientists, inspiring them to seek out bioactive compounds. Besides their medicinal properties; plants also provide essential nutrients required by the human body. Carbohydrates, proteins, fats, vitamins, and minerals present in plants play a vital role in maintaining overall health and well-being. They are involved in various physiological processes, metabolic activities, and contribute to the growth and development of the body. Regular consumption of multivitamin supplements not only enhances overall bodily functions but also improves mental and physical well-being (Radha *et al*., 2021; Petrovska,2012).

The polyherbal nutritional supplement employed in this study is purported to be a one-of-a-kind natural energy tonic derived from herbs. It is claimed to enhance overall health by providing energy through nutritional supplements, vitamins, and minerals while alleviating mental and physical stress. Polyherbal energy supplement formulation is based on aqueous extract of well reputed medicinal plants i.e *Barley, Plum, Avena sativa, Apricot, Emblica officinalis, Gotu kole, Cinnamon zelenicum* and honey. In the literature, different properties of these medicinal plants have been reported.

Emblica officinalis commonly known as Amla, it is bitter in taste having diuretic, laxatic and antipyretic properties. Amla, weighing 100 grams, contains approximately 700 milligrams of vitamin C, which is 30 times higher than the amount found in oranges. Apart from vitamin C, it is also rich in calcium, iron, protein, sugar, phosphorous, carbohydrates, alkaloids, phenolic compounds, amino acids, gallic acid, and tannic acid etc. (Muthusamy, 2008; Khan, 2009).

Avena sativa is commonly referred to as oats, is a plentiful source of various chemical components such as carbohydrates, proteins, avenanthramides, tocols, lipids, alkaloids, flavonoids, saponins, and sterols (Singh *et al*., 2013). α-Tocotrienol (vitamin E) is the major tocol present in oats, natural antioxidant present and exist as lipid soluble compounds (Peterson, 2001)

Cinnamomum verum , a widely utilized medicinal herb, serves various pharmacological purposes. It has been documented to possess valuable attributes, including anti-diabetic, antibacterial, antioxidant, anti-inflammatory, and anticancer effects. Each of these properties plays a crucial role in promoting human health and well-being (Pathak and Sherma, 2021).

Centella asiatica commonly known as Gotu Kola, has been reported to possess neuroprotective effects and a diverse range of biological activities essential for human health. These include wound healing, anti-inflammatory, antipsoriatic, antiulcer, hepatoprotective, anticonvulsant, sedative, immunostimulant, cardioprotective, antidiabetic, cytotoxic and antitumor, antiviral, antibacterial, insecticidal, antifungal, antioxidant properties, as well as applications in lepra and venous deficiency treatments (Haleagrahara & Ponnusamy 2010, Boju Sun *et al*., 2020).

Medicago sativa known as the "father of all foods" (al-fal-fa), traditionally, it has been employed to enhance memory , alleviate kidney pain, cough, muscular discomfort, and disorders of the central nervous system (CNS). This is acknowledged for its antidiabetic, antioxidant, anti-inflammatory, antifungal, anti-asthmatic, antimicrobial, and diuretic properties (Kundan and Sherma, 2011).

Prunus armeniaca referred to as the apricot, this fruit is highly abundant in micronutrients, proteins, dietary fibers, sugars, fatty acids, volatile compounds, carotenoids, phenolics, and lignans. It has been utilized medicinally to address various health concerns, encompassing respiratory, gynecological, and digestive disorders. The apricot is also renowned for its reported antipyretic, anti-inflammatory, hepatoprotective, neuroprotective, antihyperlipidemic, analgesic, immunomodulatory, and anticancer attributes (Alajil *et al*., 2021).

Withania somnifera. Traditionally, it is employed for the treatment of polyarthritis, rheumatoid arthritis, lumbago, painful inflammations, spermatorrhea, asthma, leucoderma, general debility, sexual debility, anxiety neurosis, marasmus, scabies, ulcers, and leucorrhea. Furthermore, it aids in alleviating chronic fatigue, dehydration, bone frailty, impotence, convalescence, and muscle tension (Qamar Uddin *et al.*, 2012).

Carissa grandiflora: Commonly known as plum, is utilized in the development of therapeutic remedies aimed at managing oxidative stress and associated health ailments like cancer and inflammation. Due to its diverse medicinal properties, plum is extensively incorporated within the traditional Ayurvedic system of medicine. The documented medicinal attributes of plum are attributed to the presence of alkaloids, flavonoids, saponins, cardiac glycosides, triterpenoids, and phenolic compounds, all possessing potent biological and pharmacological activities (Mehmood *et al*., 2021).

Honey, a natural substance rich in sugars, is produced by bees from flower nectar. It serves as a sweetener, a complete food, and a medicinal supplement. Comprised mainly of water and carbohydrates, honey also contains trace amounts of minerals and vitamins, including niacin, calcium, copper, riboflavin, iron, magnesium, potassium, and zinc. Additionally, honey is a source of flavonoids and phenolic acids, which act as antioxidants, neutralizing harmful free radicals within the human body. These antioxidants likely contribute to honey's anti-inflammatory properties. Honey has also demonstrated efficacy in treating stomach ulcers and possesses potent antibacterial characteristics (Sampath Kumar *et al.*,2 010).

In the current study, we followed the acute oral toxicity and preclinical studies in evaluating any toxic effect and efficacy of the Poly malt nutritional supplement. This study was conducted to authenticate the safe prescription and use of this poly herbal multivitamin supplement as a natural herbal energizer. This product may reveal more uses if they are researched on modern scientific lines.

MATERIAL AND METHODS

Test drug

The test sample was collected from the local market of Karachi (manufactured by Real Herbal Laboratories, Karachi), in 200 gram packing.

Selection of animals

Albino rats of Wistar strain of either sex weighing from 150-180g reared at animal house of PCSIR Laboratory Complex, Karachi were selected and grouped accordingly for acute oral toxicity study while rabbits of either sex weighing between 1.5-2kg were used for efficacy study. The experimental animals were housed at 25 ± 2 °C temperature and were adapted for 5 days before the experiment during which they were exposed to 12 h light/dark cycle. During acclimatization and study periods the animals were given water and food pellets *ad libitum.*

Acute Oral Toxicity Assay

Acute oral toxicity of poly- malt was determined in mice following OECD guidelines No 423. Fasted animals (provided only water) for 12 hours were randomly divided into 4 groups (n=3). Group I, II and III served as test groups and received test drug at a single dose of 300, 2000 and 5000 mg/kg body weight orally by

means of feeding cannula respectively, while at same time group VI served as control group and received vehicle (distal water).

Observation (Behavioral pattern and body weight)

All animal groups were carefully observed for the initial 30 minutes, followed by a 4-hour period to assess any immediate toxic effects. Subsequently, regular intervals of observation were maintained for 72 h, spanning a total duration of 14 days. Throughout this period, mortality rates were noted, and various laboratory findings such as body postures, movements, rearing, tremors, touch response, and any variations in skin color, mucous membrane, and pupil dilation were recorded within the initial four hours and continued thereafter for the entire 14-day period of dose administration. Additionally, the animals' weight and dietary behavior were diligently monitored and documented, as presented in Table 2 and 3. At the conclusion of the study, the animals were euthanized, and their major organs, including the liver, spleen, kidneys, and lungs, were examined for any abnormal changes in comparison to the control groups.

Body Weight

The initial weights of each animal were measured prior to administering the test substance, and subsequent weekly measurements were taken thereafter. No significant decrease in body weights was observed throughout the 14-day observation period in the animals that survived.

Efficacy Studies

In the efficacy study, a total of 24 rabbits, consisting of 12 males and 12 females, were carefully chosen and divided into two groups (n = 12). Group I served as the test group and received the test drug at a dosage of 400mg/kg of body weight, twice daily. On the other hand, group II served as the control group and received only normal feed, comprising items such as grams, bread, cucumber, carrot, etc. The following parameters were utilized for evaluating the effectiveness of the treatment.

Effects of the test drug on body weight

In this study, the test group received a Malt supplement at a dosage of 400mg/kg of body weight, administered twice daily for a period of 30 days. The impact on the animals' (both male and female) body weight and health conditions was observed and documented. Prior to commencing the experiment, the weight of each animal was recorded, and at 15-day intervals throughout the study, subsequent weight measurements were taken. The mean body weight of the test group was then calculated and compared to that of the control group.

Hematological Parameters

Blood samples were obtained from the marginal ear vein of animals in each group on the initial day and after 30 days of treatment. These samples were subjected to analysis to determine various blood parameters, including hemoglobin levels, clotting time, RBC count, MCH (mean corpuscular hemoglobin), MCV (mean corpuscular volume), and MCHC (mean corpuscular hemoglobin concentration). The analysis was performed in duplicate to ensure accuracy and reliability of the results.

Biochemical Parameters

The study aimed to evaluate the potential toxic effects of the drug on liver function and structure. To assess this, blood samples from animals in each group were collected at the beginning and after 30 days of the study. Various parameters were investigated, including serum enzyme levels of glutamic oxaloacetate (SGOT) and glutamic pyruvate transaminase (SGPT), which were measured using the calorimetric determination of transaminases Kit (TGO) from Biometrix, utilizing the Boehringer Mannhein Photometer 4010. Additionally, total bilirubin, alkaline phosphatase, random glucose, total protein, albumin, and globulin levels were determined using standard methods (Table 3).

Statistical Analysis

Results were expressed as Mean ± S.M.E. The data were analyzed by student *t*-test and *p*-value. The mean data was considered to be significant at $p \leq 0.5$.

RESULTS AND DISCUSSION

The acute oral toxicity test was conducted on albino rats, wherein different doses of the test material at 300, 2000, and 5000 mg/kg body weight were administered. No mortality was observed throughout the 14-day

observation period. The animals in both the control and treated groups exhibited normal behavior, including alertness, restlessness, normal skin color, appropriate touch response, pain response, corner sitting, righting reflux, gripping, pinna reflex, corneal reflex, as well as normal food and water intake. None of the groups showed any signs of acute toxicity such as tremors, convulsions, writhing, urination, diarrhea, salivation, lacrimation, or coma. Furthermore, the gross necropsy findings did not reveal any adverse effects on the organs in the treated groups compared to the control group. The kidneys and livers were examined for weight, volume, and appearance, and no significant differences were noted. According to OECD guideline No. 23, the administration of the maximum dose of 5000 mg/kg did not induce any signs of toxicity or mortality in rats throughout the observation period, suggesting that the polyherbal multivitamin formulation is safe and non-toxic. As per Clarke and Clarke, substances with an LD50 of 1000 mg/kg body weight (oral route) are considered safe or of low toxicity (Clarke, 1977).

Table 1. Nutritional Composition of Polyherbal Supplement**.**

S.No.	Nutritional Ingredients	Quantity per pack
1.	Vitamin C	**18.05**
2.	Vitamin E	0.38 mg
3.	Iron	0.79 mg
4.	Protein (N×6.25)	1.23 mg
5.	Calcium	0.54 mg
6.	Zinc	0.05 mg

Table 2. Mean Body Weight of Rabbits in Efficacy Study.

S.No.	Observation	Control Group Male	Control Group Female	Test Group Male	Test Group female
1.	Oral dose of drug	Only placebo	Only placebo	400mg/kg	400mg/kg
2.	No. of animals	06	06	06	06
3.	Avg. weight of animals before treatment (kg)	1.50 ± 0.01	1.70 ± 0.01	1.50 ± 0.03	1.62 ± 0.02
4.	No. of days for treatment	30	30	30	30
5.	Avg. weight of animals after treatment (kg)	1.94 ± 0.08	2.12 ± 0.17	2.45 ± 0.08	2.45 ± 0.05
6.	Difference in weight after 30 days(kg)	0.44	0.42	0.95	0.83
7.	% Increase in weight	29.33	24.70	63.33	51.23

During the 30-days efficacy study, significant beneficial effects on various aspects of health, including growth, erythropoiesis (formation of red blood cells), body weight, and other physiological functions of the body were observed. No unusual changes in behavior or locomotor activity in animals that received the test drug were found. No signs of ataxia (loss of muscle coordination) or intoxication were observed; indicating that the drug did not have any negative impact on these parameters. The food consumption of both male and female rabbits in all the groups was similar, suggesting that the intake of food and its utilization were not affected by the test drug. This indicates that the drug did not disrupt the normal feeding patterns or overall appetite of the animals. Throughout the study, all animals in the different groups appeared normal, alert, and active in their responses. The plants utilized in the formulation of the test drug contain a variety of biologically active amines, bioactive polysaccharides, trace elements, minerals, vitamins, and other components (as shown in Table 1). These constituents not only contribute to the nourishment of tissues but also impact the body weight of both male and female animals, as observed in comparison to the standard and control groups. The effect of the polyherbal multivitamin on body weight was found to be dose-dependent, and the results are documented in Table 2. In terms of biochemical parameters, the levels of serum enzymes such as glutamic oxaloacetate (SGOT) and glutamic pyruvate transaminase (SGPT), total bilirubin, alkaline phosphatase, random glucose, total protein, albumin, and globulin were found to be similar to those of the control group. This indicates that during long term study of 30 days polyherbal vitamin supplement did not produce any awful effect on liver function as mentioned in Table 3. These findings collectively indicate that the poly herbal test drug has a positive impact on health without causing any significant adverse effects in terms of behavior, locomotor activity, feed intake, or mortality. The study clearly indicates that the administration of the test drug over an

extended period has a positive impact on liver function, as evidenced by the increase in hemoglobin concentration, RBC count, PCV, and normal clotting time as information is summarized in Table 4. The animals in the test group displayed increased activity levels, higher energy levels, and improved diet intake compared to the control group. Additionally, the test drug acted as a mood stabilizer, contributing to a balanced emotional state. Furthermore, it supported a healthy immune system function. The test drug enhanced the body's capacity to sustain physical exertion and aided in adapting to different types of stress. The plants used in this multivitamin formulation has been tremendously used for anti-stress, tonic, insomnia and nervous breakdown (Machiah, 2006) also used for Alzheimer'sdisease (Song *et al*., 2018) and Parkinson's disease (Nataraj *et al*., 2017b).

Table 3. Mean Results of Biochemical Analysis in Rabbit Blood.

Sr. No	Observation	Test Group				Control Group			
		Male		Female		Male		Female	
	Day	Initial	After 30 Days	Initial	After 30 Days	Initial	After 30 Days	Initial	After 30 Days
1.	Total Bilirubin (mg/dl)	0.62 ± 0.04	0.61± 0.04	0.65 ± 0.03	0.63 ± 0.03	0.62 ± 0.04	0.64 ± 0.01	0.68 ± 0.02	0.70 ± 0.05
2.	Direct Bilirubin (mg/dl)	0.16 ± 0.01	0.15 ± 0.02	0.15 ± 0.02	0.18 ± 0.01	0.17 ± 0.01	0.16 ± 0.01	0.16 ±0. 01	0.17 ± 0.01
3.	SGPT (IU/lit)	84.2 ± 1.03	84.01± 1.5	73.9 ± 2.7	73 ± 2.1	86.9 ± 2.4	87.5 ± 3.0	81.5 ± 2.24	80.0 ± 1.4
4.	Alkaline Phosphatase (IU/lit)	129.6 ± 2.8	142.16 ± 2.3	97.8 ± 2.31	93.3 ± 3.1	124 ± 4.34	126 ± 3.4	107.16 ± 4.7	103.1 ± 3.8
5.	Glucose Random (mg/dl)	91± 5.3	88.6 ± 5.6	104 ± 2.8	103.8 ± 5.4	99.16 ± 3.9	94.5 ± 6.3	106.16 ± 3.4	104 ± 3.4
6.	Total Protein (g/dl)	6.26 ± 0.35	6.78 ± 0.24	7.06 ± 0.25	7.24 ± 0.21	6.45 ± 0.35	6.88 ± 0.24	7.13 ± 0.24	7.2 ± 0.25
7.	Albumin (g/dl)	4.5 ± 0.32	3.9 ± 0.20	4.3 ± 0.35	4.8 ± 0.12	4.4 ± 0.28	4.2 ± 0.31	4.5 ± 0.24	4.6 ± 0.24
8.	Globuline (g/dl)	1.75 ± 0.18	2.81 ± 0.29	1.96 ± 0.21	2.85 ± 0.24	1.85 ± 0.10	2.25 ± 0.20	2.1 ± 0.19	2.5 ± 0.20

Table 4. Mean Values of Hematological Parameters.

S. No	Observation	Test Group				Control Group			
		Male		Female		Male		Female	
	Day	Initial	After 30 Days	Initial	After 30 Days	Initial	After 30 Days	Initial	After 30 Days
1.	Clotting Time (min)	2.48 ± 0.02	2.55 ± 0.02	2.15 ± 0.01	3.23 ± 0.02	1.58 ± 0.15	1.60 ± 0.06	1.6 ± 0.07	1.68 ± 0.10
2.	Prothrombin Time (min)	2.41± 0.02	3.1± 0.08	3.10± 0.07	3.2± 0.04	2.47± 0.06	2.48 ± 0.06	2.2 ± 0.07	2.8 ± 0.26
3.	Erythrocyte sedimentation rate/hour	0.9 ± 0.01	1.02 ± 0.07	0.67± 0.01	0.87 ± 0.01	0.55 ± 0.07	0.58 ± 0.03	0.85 ± 0.16	1.0 ± 0.04
4.	Blood density	1.09 ± 0.04	1.09 ± 0.01	1.07 ± 0.01	1.07± 0.01	1.07 ± 0.07	1.06 ± 0.07	1.05 ± 0.07	1.03 ± 0.07
5.	Hemoglobin %	93.2 ± 0.44	96.3 ± 0.30	83.8 ± 0.21	86.9 ± 0.17	90.2 ± 0.07	91.8 ± 0.07	80.61 ± 0.07	81.2 ± 0.07

6.	RBC%	86.36± 0.72	90.85± 0.14	80.85± 0.19	83.8 ± 0.22	83.07 ± 2.1	83.16 ± 0.5	80.50 ± 0.6	80.90 ± 0.5
7.	WBC Count(gm/dl)	8051 ± 6.11	9370 ± 16.69	7590 ± 38.42	8120 ± 66.35	8042 ± 55.84	8109 ± 74.30	7470 ± 86.16	7430 ± 61.18
8.	Mean corpuscular volume (μ^3) MCV	55.93 ± 0.22	56.97 ± 0.48	57.33 ± 0.40	59.23 ± 0.22	58.60 ± 0.76	59.7 ± 0.42	57.0 ± 0.41	58.3 ± 0.82
9.	Mean hemoglobin% concentration (MHC)	18.35 ± 0.38	18.68 ± 0.52	17.66 ± 0.47	18.80 ± 0.40	18.96 ± 0.29	19.12 ± 0.15	18.66± 0.18	19.13± 0.43
10.	Mean Corpuscular Hemoglobin Conc (MCHC)	33.10 ± 0.28	32.38 ± 0.34	31.00 ± 0.40	31.45 ± 0.68	32.87 ± 0.35	32.64 ± 0.19	31.23 ± 0.58	32.34 ± 0.36
11.	Volume index	1.02 ± 0.04	1.05 ± 0.01	1.03 ± 0.03	1.08 ± 0.02	1.12 ± 0.21	1.30 ± 0.28	1.05 ± 0.10	1.06 ± 0.02
12.	Color index	1.05 ± 0.02	1.07 ± 0.03	1.05 ± 0.03	1.09 ± 0.02	1.12 ± 0.07	1.1± 0.12	1.05 ± 0.03	1.09 ± 0.02
13.	Saturation Index	1.0 ± 0.07	0.98 ± 0.18	1.01 ± 0.05	1.02 ± 0.05	0.98 ± 0.06	1.04 ± 0.11	1.03 ± 0.05	1.04 ± 0.04

The majority of plants incorporated into the formulation possess antioxidants, which are deemed crucial for sustaining long-term good health and safeguarding the body against the impacts of disease and aging. Key antioxidants found in these plants include Vitamin C, Vitamin E, B-Carotene, as well as other beneficial compounds such as flavonoids, polyphenols, and essential minerals like selenium, zinc, iron, and copper. These antioxidants play a vital role in shielding the body from the harmful effects of free radicals (Saranya *et al.,* 2017). The inclusion of plants in one's diet provides essential micronutrients such as vitamins (A, B, C, E, and K), minerals, amino acids, and fatty acids, all of which contribute to their notable nutritive value. (Xi, W 2020).

Literature survey supports to effectiveness of the test drug as an energetic tonic with many other benefits for protecting and maintaining better life expectancy. This investigation conducted on the poly herbal test drug available in the local market suggests that it has health-protective properties.

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(*Accepted for publication September 2023*)