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Research paper

ANTI-CANCER ACTIVITY OF *CEDRUS DEODARA* IN 1,2- DIMETHLY HYDRAZINE (DMH) INDUCED ANTI CANCER MODEL IN RATS

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Cancer is a dangerous disease of all multicellular organisms. Cancer is a serious as well as life threatening disease characterized by uncontrolled division and growth of abnormal cells in the body. In present study anti cancer potential of traditional herbal *Cedrus deodara* were studied in 1,2- dimethly hydrazine (DMH) induced anti cancer model. Various biochemical parameters were evlautaed such as Alakaline phosphate, Aspartate aminotransferase, Alanine aminotransferase and Histology of Liver tissue were examined. Data of the study revealed that significant depletion of biochemical markers in DMH-untreated rats as compared with control rats throughout the experimental period. This depletion might because the extract treated group shows improvement level in rats treated with DMH showed significant decrease, as a result levels of antioxidant enzymes decreased. Also DMH produces free radicals in blood, liver and the large intestine of experimental models .

KEYWORDS- Cancer, DMH , anti cancer model, biochemical markers

INTRODUCTION

Cancer is known to be a very complex disease. It is one of the leading causes of death worldwide which can damage or affect any part of the body[28]. It has been estimated that the overall new cases of cancer will rise from million in year 2000 by approximately 25% in each decade which can reach 24 million new cases per year in the year 2050,death will be rise from 6 million in year 2000 to 10 million in 2020 to over all 16 million in the year 2050; 17 million cases in world developed countries and 7 million new cases in more developed countries.

Various approaches have been employed singly or in combination in the treatment deadly disease cancer. These may include chemotherapy, Radiotherapy, surgery and immunotherapy.

Current Indian population is 1,270,272,105(1.27 billion) incidence of cancer in India is 70-90 per 100, 00 population and its prevalence is established to be around 2,500,000 (2.5 billion) with over 800,000 new cases and 5, 50, 000 death occurring each year. It is estimated that more than 70% of cases are seen in advanced stages. About 6% of all death in India are due to cancer which contribute to 8% of global cancer mortality.According to ICMR (India council of medical Research), in males most common cancer are mouth, pharynx, oesophagus, stomach, lungs. The common cancers in female are cervix, breast, mouth, and oesophagus.

Types of cancer

Carcinomas Cancer derived from epithelial cells, This group includes many of the most common cancers and include brest, prostate, lung pancreas and colon.

Sarcomas Cancer derived from connective tissue i.e. bone, cartilage, each of which develops from cells originating in mesenchymal cells outside the bone marrow.

Lymphomas leukaemias There two classes arise from hematopoietic blood forming cells,that leave the marrow and tend to mature the lymph and blood.

There are said to be more than 200 different types of cancer some of them are- Anal cancer, bladder cancer, bone cancer, breast cancer, cervical cancer, kidney cancer, leukaemia, liver cancer, prostate cancer, vaginal cancer, Pancreatic cancer, lymphoma, stomach cancer, testicular cancer, colon cancer etc.

The ultimate goal in treating patients with cancer is to be able to cure their disease with a combination of treatment and potential metastases. Most common classes of drugs are administered with the intent of controlling the disease or the symptoms caused by disease.

Herbal plants posses anti-cancer potential

World health organisation estimates that 80% of the world population relies on herbal medicines. Synthetic drugs may cause and undesirable effects· Were as natural products are considered safe and effective, Herbal medicines are popular for improving life with no side effects. As we know cancer is second leading cause of death worldwide. Natural therapies such as use of plant derived products in cancer treatment may act as boon. Currently few plants and their products are used to treat cancer.

MATERIAL AND METHODS:

Anti cancer activity 1,2- dimethly hydrazine (DMH) induced anti cancer model

The tumour incidence can be modulated by the amount of carcinogen administered and the number of applications. With increasing doses of the carcinogen, the latency period decreases and the tumour incidence increases. Usually carcinogen at a dosage of 15-25 mg/kg body weight per week is administered subcutaneously . In our studies DMH at a dosage of 15-25 mg/kg-body weight was injected subcutaneously once a week, for 15-20 weeks consecutively.Besides the colorectal tumours, the small bowel tumours are also induced but in much lower incidence. However, small bowel tumorigenesis is characteristic of high-dose regimens of DMH.27 Small intestinal tumours are mostly well or poorly differentiated adenocarcinomas.5,8,11 Well-differentiated adenocarcinomas only occasionally demonstrate invasion through the intestinal wall and into the adjacent tissues. On the other hand the poorly differentiated type is more aggressive and mostly metastasises to the mesenteric lymph nodes and in advanced stages frequently develops carcinosis of peritoneum or conglomerate tumours in the area between the duodenum, stomach, hilus of the liver and affected small intestine.Extraintestinal tumours may also be induced by DMH. Some rats develop tumours of Zymbal's gland (auditory sebaceous glands), usually squamous cell carcinoma.

The animal were divided in to five groups in which six

animal each

Group I: 2% Tween-80 (5ml/kg b. wt, i.p.)

Group II: DMH (2X10^6 cells/rat) + 2% Tween-80 (5ml/kg b. wt, i.p.)

Group III: DMH (2x10^6 cells/rats) + hydroalcoholic extract of *Cedrus Deodara* (250mg/kg b. wt, i.p.)

Group IV: DMH (2x10^{6}cells/rats) + hydroalcoholic extract of *Cedrus Deodara* (500mg/kg b. wt, i.p.)

Group V: DMH (2x10^{6}cells/rat) + 5-fluorouracil (20mg/kg b. wt, i.p.

After 10th day of drug therapy the following biochemical parameters were evaluated for anti cancer potential of hydroalocholic extract of *Cedrus Deodara*

Determination of Tissue Enzyme Assay

Alkaline Phosphatase (ALP):

The method described by Bassey et al. as modified by Wright et al. using Randox kits. In a cuvette, 10 µl of sample was mixed with 500 µl of the reagent. The initial absorbance was read at 405 nm, and subsequently over 3 minutes. The mean absorbance per minute was used in the calculation:

ALP activity (IU/l) = 2742 × ΔA 405 nm/min;

Where: 2742 = Extinction coefficient;

ΔA 405 nm/ min = change in absorbance per minute for the homogenate sample.

Alanine transaminase (ALT) activity:

The method described by IFCC using Randox kits was used. 50 µl of the sample and 500 µl of the ALT reagent were mixed in a test tube, and the initial absorbance at 340 nm was read after 1 minute. The timer was started simultaneously and further readings of the absorbance were taken after 1, 2, and 3 minutes.

ALT activity (nm/min) = 1746 × ΔA 340 nm/min,

ΔA 340 nm/min = change in absorbance per minute for the homogenate sample,

1746 = Extinction coefficient.

Aspatate transaminase (AST) activity:

The same assay method described for ALT was used with the exception that the ALT reagent was replaced with the AST reagent.

AST activity (nm/min) = 1746 × ΔA 340 nm/min;

ΔA 340 nm/min = change in absorbance per minute for the homogenate sample;

1746 = Extinction coefficient.

Determination of serum alkaline phosphatase (ALP):

The substrate p-nitrophenyl phosphate is hydrolyzed by alkaline phosphatase from the sample in the presence of magnesium ions, to form nitrophenol which is yellow and can be read at 405 nm. The intensity of color produced is proportional to the activity of alkaline phosphatase.

The procedure described by Bassey et al.using Randox kits was used for the assay. In a cuvette, 10 µl of sample was mixed with 500 µl of the reagent.

The initial absorbance was read at 405 nm, and subsequently over 3 minutes.

The mean absorbance per minute was used in the calculation:

ALP activity (IU/l) = 2742 × ΔA 405 nm/min.

Where: 2742 = Extinction coefficient;

ΔA 405 nm/min = change in absorbance per minute for the homogenate sample.

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RESULT AND DISCUSSION:

Effect of standard drug and hydro alcoholic extract of *Cedrus deodara* in 1,2- dimethly hydrazine (DMH) induced cancer in rats

Tumour lesions induced by DMH. DMH is highly specific for colonic epithelium and induces tumours mostly in large bowel. Colon specific susceptibility for this carcinogen is a result of a delayed or incomplete repair of damaged DNA in the colon compared to other organs, leading to accumulation of mutations, and in a small proportion of cells giving rise to CRC. Higher susceptibility to colon versus small intestine has been shown in experiment where segments of colon that were transposed to the middle part of small intestine developed tumours but segments of small intestine that were transposed to the colon did not. Tumours are distributed in all parts of the colon, but in a majority are observed in the distal part of colon. Gross tumours are initially detected in the distal colon at 16 weeks but in proximal colon after 22 weeks.

The tumour incidence can be modulated by the amount of carcinogen administered and the number of applications. With increasing doses of the carcinogen, the latency period decreases and the tumour incidence increases. Usually carcinogen at a dosage of 15-25 mg/kg body weight per week is administered subcutaneously.

In our studies DMH at a dosage of 15-25 mg/kg-body weight was injected subcutaneously once a week, for 15-20 weeks consecutively. Besides the colorectal tumours, the small bowel tumours are also induced but in much lower incidence. However, small bowel tumorigenesis is characteristic of high-dose regimens of DMH.27 Small intestinal tumours are mostly well or poorly differentiated adenocarcinomas.5,8,11 Well-differentiated adenocarcinomas only occasionally demonstrate invasion through the intestinal wall and into the adjacent tissues. On the other hand the poorly differentiated type is more aggressive and mostly metastasises to the mesenteric lymph nodes and in advanced stages frequently develops carcinosis of peritoneum or conglomerate tumours in the area between the duodenum, stomach, hilus of the liver and affected small intestine. Extraintestinal tumours may also be induced by DMH. Some rats develop tumours of Zymbal's gland (auditory sebaceous glands), usually squamous cell carcinoma.

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Group III: DMH ($2x10^6$ cells/rats) + hydroalcoholic extract of *Cedrus deodara* (250mg/kg b. wt, i.p.)

Group IV: DMH ($2x10^6$cells/rats) + hydroalcoholic extract of *Cedrus deodara* (500mg/kg b. wt, i.p.)

Group V: DMH ($2x10^6$cells/rat) + 5-fluorouracil (20mg/kg b. wt, i.p.)

After 20th week of drug therapy the following biochemical parameters were evaluated for anti cancer potential of hydroalocholic extract of *Cedrus deodara*

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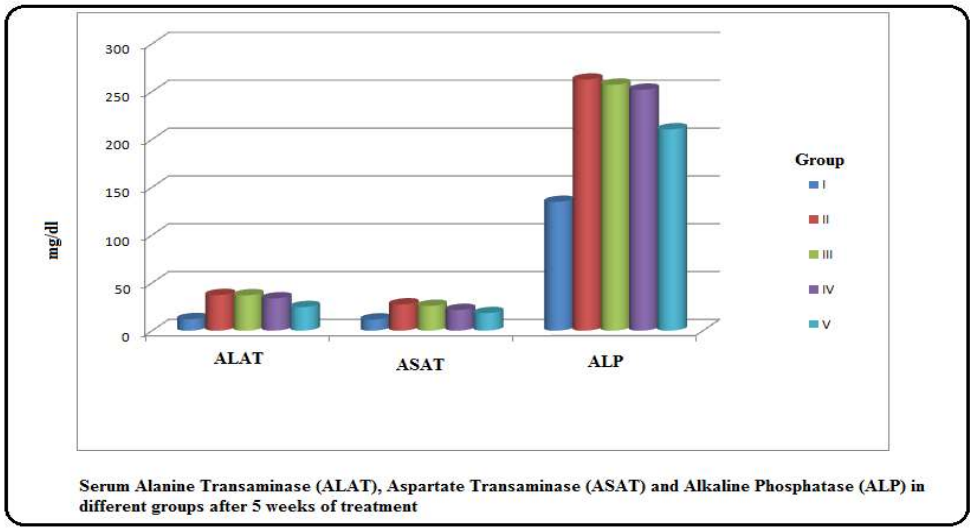
International Journal of Pharmaceutical Erudition

Table 1 Serum Alanine Transaminase (ALAT), Aspartate Transaminase (ASAT) and Alkaline Phosphatase (ALP) in different groups

Group	ALAT (values after weeks of treatment)			ASAT (values after weeks of treatment)			ALP (values after weeks of treatment)		
	5	10	20	5	10	20	5	10	20
I	12 ± 1.02	11.7 ± 0.91	12.48 ± 0.82	11.6 ± 0.57	12.8 ± 0.53	13.6 ± 0.31	134.6 ± 2.74	126.3 ± 0.84	121.7 ± 1.42
II	37.2 ± 2.37	54.3 ± 1.68	76.9 ± 2.46	27.4 ± 2.26	45.2 ± 2.94	48.3 ±	262.4 ± 2.86	291.6 ± 1.58	305.8 ± 2.63
III	36.9 ± 2.59	52.8 ± 1.74	68.2 ± 2.96	25.9 ± 1.48	37.4 ± 2.05	31.9 ± 1.56	257.1 ± 2.18	241.3 ± 1.26	236.2 ± 2.37
IV	33.7 ± 1.96	51.8 ± 1.29	57.6 ± 1.35	21.6 ± 2.08	34.1 ± 1.74	26.5 ± 1.87	251.8 ± 2.39	227. 2 ± 2.86	214.9 ± 1.64
V	24.6 ± 1.28	42.6 ± 1.94	27.4 ± 2.07	18.3 ± 1.68	17.35 ± 1.37	14.83 ± 2.48	210.4 ± 2.93	179.5 ± 2.41	144.3 ± 1.03



Histogram: 1 Serum Alanine Transaminase (ALAT), Aspartate Transaminase (ASAT) and Alkaline Phosphatase (ALP) in different groups after 5 weeks of treatment

SUMMARY AND CONCLUSION:

Data of the study revealed that significant depletion of biochemical markers in DMH-untreated rats as compared with control rats throughout the experimental period. This depletion might because the extract treated group shows improvement level in rats treated with DMH showed significant decrease, as a result levels of antioxidant enzymes decreased. Also DMH produces free radicals in blood, liver and the large intestine of experimental models In the present study, severe increase in serum ALAT, ASAT and ALP activities were observed in DMH-untreated rats as compared with control rats, and the

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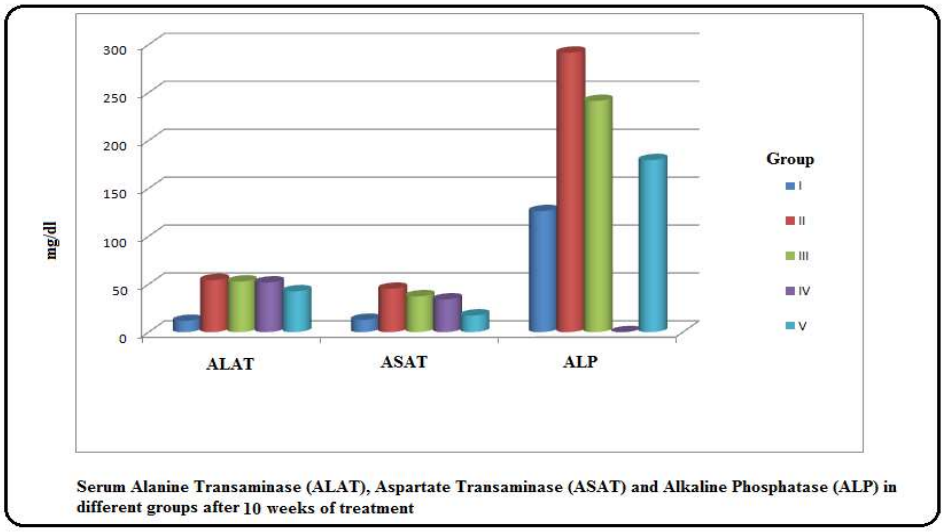
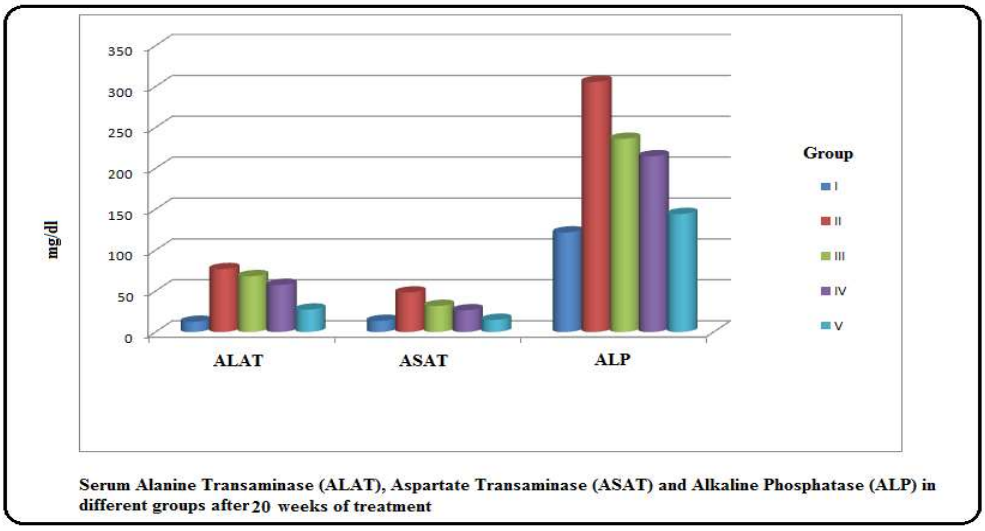


Histogram: 2 Serum Alanine Transaminase (ALAT), Aspartate Transaminase (ASAT) and Alkaline Phosphatase (ALP) in different groups after 10 weeks of treatment



Histogram: 3 Serum Alanine Transaminase (ALAT), Aspartate Transaminase (ASAT) and Alkaline Phosphatase (ALP) in different groups after 20 weeks of treatment

maximal ALAT, ASAT and ALP activities were noted in the 20th week. The increase in serum enzymes (ALAT & ASAT) activities might be due to the loss of cellular functional integrity of hepatocytes membrane resulted from highly reactive electrophiles i.e., carbonium ions and alkyl free radicals which severely damage the liver causing necrosis and fatty infiltration, methylate nucleobases and disrupt the polysomal assembly and hence enzymes that are located in liver cells leak out and make their way into the general circulation.

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