The Journal of Phytopharmacology 2015; 4(6): 282-286
Online at: www.phytopharmajournal.com

Research Article

ISSN 2230-480X
JPHYTO 2015; 4(6): 282-286
November- December

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Chemopreventive efficacy of different doses of *Ferula asafoetida* oleo-gum-resin against 1,2-dimethylhydrazine (DMH) induced rat colon carcinogenesis

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ABSTRACT

Colon cancer is the third most common malignant neoplasm in the world and it remains an important cause of deaths, especially in western countries. Its etiology is known to be a combination of hereditary, environmental, dietary factors and lack of physical activity. Chemoprevention through dietary intervention is an emerging option to reduce mortality due to colon cancer. The present study was aimed to investigate the chemopreventive potential of different doses of *Ferula asafoetida* oleo-gum-resin on 1,2-dimethylhydrazine (DMH) induced rat colon carcinogenesis by evaluating tumor multiplicity, tumor incidence, and tumor size, Serum total sialic acid levels as well as histoarchitecture of colons of rats subjected to various treatment. Rats were randomly divided into six groups. Group I rats served as control. Group 2 rats received DMH (30 mg/kg body weight (bw)) for 16 weeks. Group 3-5 animals received asafoetida daily at a dose level of 5mg/100gm bw, 10mg/100gm bw and 20mg/100gm bw respectively along with weakly DMH injections. Group 6 rats received asafoetida daily (20mg/100g bw daily) for 16 weeks. Increased tumor incidence and multiplicity was observed in DMH treated rats which were decreased with asafoetida supplementation. Asafoetida at the dose of 10mg/100gm bw had shown profound beneficial effects by exhibiting near normal Total Sialic Acid levels and well-preserved colon histology. These findings suggest that asafoetida dose 10mg/100g bw is minimum dose with maximum protection for colon cancer.

Keywords: Colorectal cancer, Dimethylhydrazine, *Ferula asafoetida*, antioxidants, Total sialic acid.

INTRODUCTION

Colon cancer is the third most common problem faced by medical fraternity around the world [1]. It is still a leading cause of cancer death in Asia and western countries [2]. Chemoprevention refers to the use of natural or synthetic compounds to prevent, reverse, or delay the development of cancer [3]. Life style modification can prevent more than two-thirds of the cancers, nearly one-third of these cancer occurrences can be prevented by taking a balanced diet alone [4]. Cancer is strongly influenced by various environmental factors, with diet being one of the major modifying agents [5]. High fat and low carbohydrate diets have been found to have increased the risk of colon cancer incidence and mortality [6]. Studies also support the concept that dietary habits, such as high intake of fruits and vegetables, can reduce the risk of developing colorectal cancer [7]. Because food-derived products exist universally and are expected to be safe, they are highly interesting for development as chemopreventive agent [8]. Progress in chemoprevention research has brought about innovative approaches to the prevention and control of colon cancer.

Chemically-induced models of colon carcinogenesis in rodents have been suitable for the study of risk factors, prevention and tumor development [9]. Experimental colon cancer induced by DMH in rats mimic human colon cancer and is therefore, an ideal model for chemoprevention studies [10]. The cells at the subcutaneous site do not possess enzymes capable of reacting with DMH. Hence, subcutaneously injected DMH reaches the liver via circulation, and gets metabolizedinto various intermediates such as azoxymethane (AOM) and methylazoxymethanol (MAM) [11]. Later on MAM is transported to the colon via bile or blood to generate its ultimate carcinogenic metabolite, electrophilic methyldiazonium ion, which in turn generates carboniumion that is responsible for the methylation of nucleic acids that triggers colon carcinogenesis [12]. The active metabolites of most carcinogens are thought to evoke the formation of oxygen-derived free radicals and intermediates of oxygen products such as hydrogen peroxides. It has also been reported that DMH produces free radicals that induce oxidative DNA damage in the liver and colon [13].

Natural products with diverse pharmacological properties are gaining more attention in the prevention and treatment of various diseases including cancer. Natural dietary products consist of a wide variety of biologically active phytochemicals which have been shown to suppress early and late stages of

carcinogenesis [14]. Asafoetida is an oleo-gum-resin obtained from the exudates of the roots of the Iranian endemic medicinal plant, *Ferula asafoetida*. Asafoetida has been used as a spice and a folk phytomedicine for centuries. Traditionally it is being used for treatment of respiratory and nervous disorders. Recent pharmacological and biological studies have also shown several activities, such as antioxidant [15], cancer chemopreventive [16], anti-diabetic [17], antispasmodic and hypotensive [18] from this oleo-gum-resin. Till date no studies are available demonstrating the colon cancer chemopreventive efficacy of *Ferula asafoetida* gum resin extract using an in vivo model of colon cancer. This study provides the scientific evidence for the chemopreventive potential of asafoetida against DMH induced colon carcinogenesis by evaluating lipid peroxidation, antioxidant profile ad histopathology in experimental rats.

MATERIALS AND METHODS

Materials

1,2-dimethylhydrazine (DMH), was purchased from Sigma Chemicals Co., St. Louis, MO, USA. The rest of the chemicals and solvents utilized were of analytical grade and were obtained from Hi-Media Laboratories Ltd., Mumbai, India. Asafoetida of high purity grade was purchased from SSP Super Fine Asafoetida Company, Banglore, India. The dried powder of asafoetida was dissolved in doubdle distilled water overnight at room temperature, and the yielded suspension was used orally. Concentrations and dosages of the aqueous extract were expressed as crude amount of the dried oleo-gum-resin used in preparing the stock solution [19].

Animal Treatment

36 male Spargue Dwaley rats in the weight range of 120–150 gms were procured from the Central Animal House Facility of Panjab University, Chandigarh. All animals were housed in polypropylene cages stacked with a hygienic bed of husk, placed in a well-ventilated animal room under optimum hygienic conditions with ambient light and temperature. They were provided with the standard pellet diet and drinking water ad libitum. Animal care procedures followed in this study were done in accordance with the ethical guidelines for care and use of laboratory animals that were approved by Institutional Animal Ethics Committee (IAEC), Panjab University, Chandigarh, India. The animals were acclimatized to the experimental conditions for 1 week before being subjected to various treatments.

Experimental groups

To study the effect of prophylactic treatment with asafoetida on DMH induced colon cancer, animals were divided into 6 groups. Group 1 animals served as controls and received 1mM Ethylene di-amine tetraacetic acid (EDTA) saline subcutaneously every week, which was used as a vehicle in the DMH-treated group. Animals in group 2 were administered a weekly dose of DMH at a dose level of 30mg/kg body weight (bw) dissolved in 1mM EDTA normal saline (pH-6.5) [20], Group 3-5 animals were administered aqueous extract of asafoetida orally at dose levels of 5mg/100gm bw, 10mg/100gm bw and 20mg/100gm bw respectively along with weakly DMH injections. Group 6 animals were given aqueous extract of asafoetida orally daily at dose level of 20mg/100gm bw. The total period of study was 16 weeks. The animals were sacrificed after overnight fasting at the end of 16 weeks.

Record of body weights

A record of the body weights of normal control, DMH and asafoetida treated animals was kept throughout the study. The animals were weighed at the beginning of the experiment, once a week during the experiment and finally before sacrifice.

Colon tumor analysis

After 16 weeks of DMH treatment, colons were excised from the rats, blotted dry, opened longitudinally and the inner surface was examined for visible macroscopic lesions. Tumors were easily discernable in the inflamed sections of the colon. The colons were observed for tumor incidence and multiplicity studies. Tumor size was recorded using a vernier caliper with 0.1 mm graduations. The chemopreventive tumor response was assessed on the basis of tumor incidence and multiplicity, which were calculated as follows:

- Tumor incidence: percentage of animals having tumors in cancer group;
- Tumor multiplicity: mean of tumors counted in cancer group/total animals in cancer group.

Total Sialic acid (TSA)

TSA was estimated by following the method of Ghara *et al.* 2008 [21]. For TSA, 20 μL of serum samples were diluted to 1 ml using water and were then mixed with 1 ml of resorcinol reagent. This was followed by incubation of all the tubes in water for 15 min, then on ice bath for 10 min, and finally 2ml of n-butanol was added in each tube. The above reaction mixtures were then centrifuged at 2500 rpm for 10 min at room temperature. The supernatants were read at 580 nm.

Histopathological studies

Formalin fixed tissues were processed for histopathological observations at the light microscopic level. Briefly, following an overnight fixation in buffered formalin, tissues were dehydrated through ascending grades of alcohol, cleared in benzene and embedded in paraffin. Sections of 5-7 micrometer thick were cut, placed serially on clean glass slides and then de-paraffinized through descending grades of alcohol. Sections were made from each colon tissue and were stained with hematoxylin and eosin. These were then observed under a light microscope and the gross morphology was noted.

Statistical analysis

Data were presented as mean ± standard deviation of the mean (SD) of six animals per group. Data analyses were carried out using SPSS v14 (SPSS, Chicago, IL, USA). A value of $P < 0.05$ was considered as significant.

RESULTS

Body weight changes

Changes in the body weight of animals were studied during the experimental period of 16 weeks. Administration of DMH to rats for 16 weeks days resulted in statistically significant decrease in weight gain as compared to control and asafoetida treated groups. Asafoetida and DMH administration together resulted increase in body weight of rats as compared to only DMH group suggesting that asafoetida treatment ameliorated DMH-induced damage (Table 1) to overall body metabolism.

Table 1: Effect of asafoetida on body weights of animals following 16 weeks of DMH treatment

Groups	Initial body weight (gm) 1st week	Final body weight (gm) 16th week
Control	128.33 ± 16.02	279.16 ± 16.25
DMH	127.50 ± 18.37	221.50 ± 14.74 ^{a1}
Asafoetida(5mg/100gm bw) + DMH	129.16 ± 18.82	255.60 ± 15.62 ^{a2,b1}
Asafoetida(10 mg/100gm bw) + DMH	130.83 ± 10.21	260.83 ± 10.20 ^{a2,b1}
Asafoetida (20 mg/100gm bw) + DMH	129.33 ± 12.00	259.16 ± 10.48 ^{a2,b1}
Asafoetida only (20 mg/100gm bw)	131.83 ± 21.54	277.50 ± 6.89

Data is expressed as mean ± S.D., n=6 $^{a2}P < 0.05$, $^{a1}P < 0.001$ when values were compared with controls $^{b1}P < 0.001$ when values were compared with DMH treated animals

Colon tumor analysis

Table 2 shows the incidence, multiplicity and size of colonic tumor which were significantly higher in DMH alone treated rats. On supplementation with different doses of asafoetida tumor incidence, multiplicity as well as size of was lower as compared to DMH alone treated rats. The incidence of colonic tumors in rats treated with DMH and supplemented with asafoetida at the dose of 10mg/100g bw, was markedly lower as compared to the rats supplemented with 5 or 20 mg/100g bw of asafoetida when compared with DMH treated group.

Table 2: Effect of asafoetida on tumor incidence, tumor multiplicity and tumor size following 16 weeks of DMH treatment

Groups	Tumor incidence (%)	Tumor multiplicity(mean tumors/animal	Tumor Size (in cms)
Control	0	0	--
DMH	100	2.5	0.88 ± 0.01^{a}
Asafoetida(5mg/100gm bw) + DMH	66.6	1.33	$0.75 \pm 0.04^{a,b}$
Asafoetida(10 mg/100gm bw) + DMH	50.0	1.0	$0.66 \pm 0.12^{a,b}$
Asafoetida (20 mg/100gm bw) + DMH	50.0	1.17	$0.71 \pm 0.07^{a,b}$
Asafoetida only (20 mg/100gm bw)	0	0	--

Data of tumor size is expressed as mean ± S.D., n=6 $^{a}P < 0.001$ when values were compared with controls $^{b}P < 0.001$ when values were compared with DMH treated animals

Serum Total sialic Acid Levels

It was observed that Total Sialic Acid (TSA) levels in serum of rats increased significantly following DMH administration for 16 weeks as compared to control group. All dosages of asafoetida along with DMH showed significant reduction in Total Serum Sialic Acid levels when compared to DMH group. Group with asafoetida dosage 10mg/100gm bw and 20mg/100gm bw showed maximum reduction in serum TSA
(Table 3).

Table 3: Total Sialic Acid levels in serum of rats of following 16 weeks of DMH treatment

Groups	Total Sialic Acid (TSA) (mg/dl)
Control	29.66±2.29
DMH	53.41±3.46 [a]
Asafoetida(5mg/100gm bw) + DMH	44.38±1.29 [b,c]
Asafoetida(10 mg/100gm bw) + DMH	39.44±4.74 [a,c]
Asafoetida (20 mg/100gmbw) + DMH	41.16±3.96 [b,c]
Asafoetida only (20 mg/100gm bw)	32.19±2.49

Data is expressed as mean ± S.D., n=6 $^{a2}P<0.01$,$^{a1}P < 0.001$ when values were compared with controls $^{b1}P < 0.001$ when values were compared with DMH treated animals

Histopathological studies

Control rats showed normal colonic architecture with regular mucosal lining whereas rats treated with DMH for 16 weeks showed well differentiated carcinoma with irregular glands lined by cubocolumnar cells with pleomorphic hyperchromatic nuclei with loss of polarity. However, asafoetida supplementation at different concentrations along with DMH showed appreciable improvement in histoarchitecture but inflammation was observed at some locations. Supplementation of asafoetida 5mg/100gm bw to DMH treated animals showed intraepithelial lymphocytosis and inflammation. This group showed low grade dysplasia in few animals. Supplementation asafoetida 10mg/ 100gm bw observed minimum focal inflammation at some locations. Supplementation with asafoetida 20mg/100gm bw observed mild inflammation. No toxicity was observed in the group supplemented with highest of dose of asafoetida alone (20mg/100gm bw). Histoarchitecture of colon of rats supplemented with 10 mg/100gm bw and 20mg/100gm bw dosage showed more improvement in histoarchitecture when compared to 5mg/100gm bw dosage group. However the effect was more pronounced in rats supplemented with asafoetida at the dose of 10 mg/100g bw. (Fig 1. A-F)

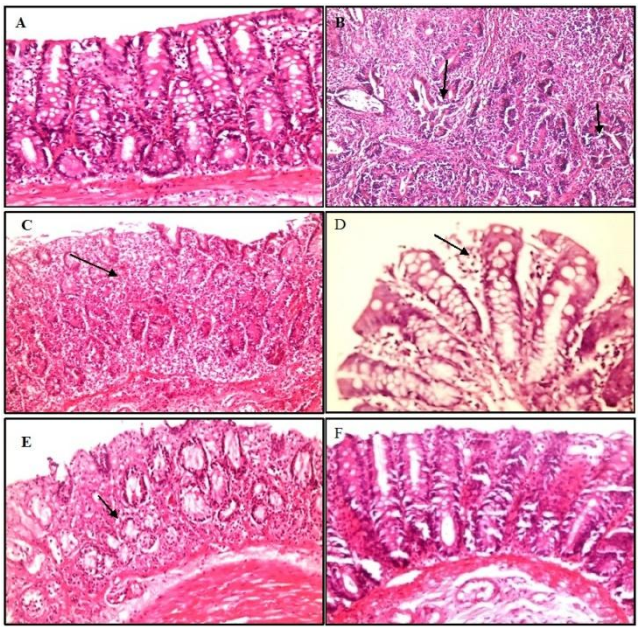

Figure 1: Effect of asafoetida on DMH induced alterations in colon histology **(A)** Colonic histoarcetecture of control rat showing normal morphology **(B)** Colonic histoarchetecture of DMH treated rat showing the well differentiated adenocarcinoma **(C)** Colon histoarchetecture of asafoetida (5mg/100g bw) supplemented DMH treated rat showing mild intraepithelial lymphocytosis and inflammation. **(D)** Colon histoarchetecture of asafoetida (10mg/100gm bw) supplemented DMH-treated rat showed minimum focal inflammation **(E)** Colon histoarchetecture of asafoetida (20mg/100gm bw) supplemented DMH treated rat showing mild inflammation **(F)** Colonic histoarchitecture of asafoetida (20mg/100gm bw) supplemented rat showing normal morphology

DISCUSSION

Protective effect of asafoetida in DMH induced colon carcinogenesis was observed during the study. The study clearly showed that the administration of asafoetida at 3 different concentration attenuates DMH induced alterations in tumor incidence, tumor multiplicity, tumor size, histoarchicecture of colons as well as total sialic acid levels in serum of rats. These findings suggest that 10mg/100gm bw dose of asafoetida was the most effective among the three different doses of asafoetida. It also suggests that asafoetida might play a promising anticancer role with respect to colon carcinogenesis.

In the present study, all the rats in the experimental groups showed an increase in the body weight throughout the study period, but increase in body weight observed after 16weeks in DMH alone treated rats was significanty lower as compared to control rats. Reduced weight gain in animals might be partially due to reduction in food intake by DMH-treated animals. Also this may be due to increased polyp burden driven cachexia [22],[23]. DMH administration to rats for 16 weeks resulted in 100% of tumor incidence and 2.8 tumor multiplicity in colon of rats which is high as compared to control rats. It has also been reported that administration of DMH increased the proliferation of the colon crypts in the test animals during early carcinogenesis, and altered the distribution of proliferating and apoptotic cells in the colon [24].

Supplementation with asafoetida by oral gavage at the dose of 10 mg/100gm bw to DMH treated rats showed increased body weight, growth rate and also significantly decreased colonic tumor incidence (50%), tumor multipliciry (1.5) and tumor size, thereby effectively reversing the DMH induced deleterious changes. This could be due to the ability of Asafoetida to counteract DMH induced carcinogenicity/tumor burden, thereby preventing cachexia. Previous reports also suggested in which DMH showed feeble carcinogenicity in the presence of potent natural phy-tochemicals [25]. Mallikarjuna *et al*., has reported reduction in the multiplicity and size in mammary tumors in rats following asafoetida supplementation [26]. Moreover, the absence of tumor incidence in rats treated with asafoetida alone suggests that asafoetida at this dose level, causes no disruption of normal cellular morphology hence is non-toxic.

The terminal sugar component of the oligosaccharide chains of glycoproteins and glycolipids is termed generically as *sialic acid* [27]. Serum total Sialic acid (TSA) levels have been used as laboratory marker test in a variety of pathological conditions. In the present study, marked elevation in serum TSA concentrations have been noted in DMH treated rats 16 weeks. Since, sialic acid are membrane components and during carcinogenesis increased cellular proliferation takes place therefore, its level is expected to increase during carcinogenesis as reported by other researchers [28]. On other hand asafoetida supplementation at all doses along with DMH decreased the level of sialic acid significantly when compared with only DMH group. Though the mechanism by which asafoetida affords a restoration of TSA towards the normal level is not clear, it might facilitate in the detoxification of DMH. Also the possible mechanisms through which asafoetida inhibited the tumorigenic events is its anti-oxidant properties [26], [29]. Phenolic compounds like ferulic acid present in it which been reported to have strong antioxidants and anti-tumor properties [30]. Ferulic acid has also been reported to inhibit of growth of human breast and colon cancer cells [31].

DMH treatment for 16 weeks in DMH resulted in well differentiated adenocarcinoma. Evidence from animal studies has shown that that experimental colonic tumors induced by DMH are of epithelial origin with a similar histology, morphology and anatomy to human colonic neoplasms [32]. Treatment with asafoetida at all dose concentrations restored the normal histoarchitecture in the colonic epithelial cells. However 10mg/100gm bw and 20mg/100gm bw doses of asafoetida showed more protective effect as compared to 5mg/100gm bw, this could possibly be because 5mg/100gm bw dose may not be sufficient to counteract the damaging effects of DMH. Histopathological observations suggest that supplementation of asafoetida under the experimental conditions can affect colon carcinogenesis by altering the efficacy at which DMH can initiate histological changes indicating its anti-carcinogenic potential. The observed modulation in histoarchitecture by asafoetida could be ascribed to its ability to maintain cell structure and integrity either by some direct mechanism or indirectly by scavenging the free radicals. However, study needs further exploration with regard to other definitive bioassays including protein expression and documentation of specific molecular markers to establish the exact mechanism for asafoetida mediated cancer chemoprevention.

CONCLUSION

Overall the findings of the present study reveals that asafoetida supplementation attenuates DMH induced deleterious effects in of rats. This is the first scientific study exploring the chemopreventive potential of asafoetida against DMH induced rat colon carcinogenesis. Although 20mg/100gm bw of asafoetida was also found to be beneficial, the medium dose of 10mg/100gm bw exhibited more pronounced effect as it constantly influenced all the biochemical parameters tested in this study. Our histological evaluation also validates the remarkable beneficial effect of the medium dose. Hence the medium dose was chosen as an optimum dose for exploring the molecular targets of asafoetida which is currently being tested in our laboratory to develop asafoetida as a promising chemopreventive agent against colon carcinogenesis.

Acknowledgement
The authors gratefully acknowledge the financial support rendered by Indian Council of Medical Research, India. (vide letter no. 3/1/3JRF-2011/HRD-26).

Conflicts of interest
There are no conflicts of interest.

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HOW TO CITE THIS ARTICLE

Panwar R, Rana S, Dhawan DK, Prasad KK. Chemopreventive efficacy of *Ferula asafoetida* oleo-gum-resin against 1,2-dimethylhydrazine (DMH) induced rat coloncarcinogenesis. The Journal of Phytopharmacology 2015;4(6):282-286.