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Research Article

IN-VIVO EVALUATION OF ORODISPERSIBLE FILM OF *ALLIUM SATIVUM* LINN. IN COLON TUMOUR INDUCED MICE

Dnyaneshwar R Pawar *, Santosh R Butle
School of Pharmacy, "Dnyanteerth", Vishnupuri, Swami Ramanand Teerth Marathwada University, Nanded, Maharashtra, India
*Corresponding Author Email: dnyanpawar9@gmail.com

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ABSTRACT

The present study emphasizes on *In-Vivo* evaluation of tumour suppressive activity of Orodispersible film formulation containing stabilized garlic extract of *Allium sativum* Linn. on colon tumour induced mice **(**Colon – 26). Initially *"In-Vitro"* activity was performed on two different cancer cell lines like human colon cancer cell line (COLO 205) and human prostate cancer cell line (PC-3). For further *"In-Vivo"* activity evaluation colon tumour induced mice **(**Colon – 26) were selected based on results of different *"In-Vitro"* cell lines studied. As compared to reference drug, Adriamycin (Doxorubicin) of allopathic origin, orodispersible film formulation containing stabilized garlic extract of *Allium sativum* of natural origin shows comparable tumour suppressive activity on long term dose. Hence orodispersible film formulation containing stabilized garlic extract of *Allium sativum* will be a useful nutraceutical for cancer prevention, mitigation and to avoid re-occurrence of cancer. Above orodispersible film formulation possesses significant anticancer activity, to warrant further tumour suppressive activity shall be done on human volunteers to determine precise safety, efficacy, pharmacokinetic and pharmaco-dynamics.

Keywords: Stabilized garlic extract**,** Orodispersible film, *"In-Vivo"* (Colon – 26), *Allium sativum.*

INTRODUCTION

Cancer is a preventable disease to an extent. Good nutrition is especially important for people with cancer. Eating well while undergoing cancer therapy will be helpful to feel better, keep up strength and energy, tolerate treatment-related side effects, heal and recover quickly. Eating well means eating a variety of foods that provide nutrients an individual needs to maintain health while fighting cancer.

Omar (2010), in his study of organosulfur compounds and possible mechanism of garlic in cancer in the Saudi Arabia have investigated the chemical components of garlic and their role in cancer, specifically colon cancer. "Several individual compounds have been isolated from garlic and two major groups of compounds that show active anticancer effects have been identified. One group is the lipid-soluble allyl sulfur compounds such as diallyl disulfide (DADS) and diallyl trisulfide (DATS), and the other one is the water-soluble compounds c-glutamyl S-allylcysteine group such as S-allylcysteine (SAC) and S-allylmercaptocysteine (SAMC). Other studies showed that S-allyl mercaptocysteine stops the growth of breast cancer cells, erythroleukemia and colon cancer cells. S-allyl mercaptocysteine prevented colon cancer cell growth by 71%, disrupting cellular microtubules that form the cytoskeleton and the mitotic spindle in cells, thus disrupting cell division. In addition, S-allyl mercaptocysteine induced cell suicide (apoptosis) in the colon cancer cells, by activating apoptosis signalling pathway enzymes, including caspase that ultimately kills the cells" (p.3).[1]

Wang (2016) in his studies of novel anticancer effect of garlic derivatives in China have reported efficacy of garlic for prevention and treatment of cancers. "Both *In-Vivo* and *In-Vitro* studies have shown that these individual compounds are not only able to suppress the skin, esophageal, stomach, colon, liver, lung and breast cancer growth in animal models, but also directly inhibit proliferation of a variety of cancer cell lines derived from colon, lung, leukemia, skin, breast and prostate cancers *In-Vitro*. These lines of evidence suggest that in addition to their cancer preventive effect, the garlic derivatives may also be used as effective agents in the treatment of human primary cancers."(p.1) [2]

Recently Xiao *et al* (2003) in his studies on induction of apoptosis by the garlic-derived compound reported "that the garlic derivative S-allylmercaptocysteine (SAMC) inhibits growth, arrests cells in G_2-M, and induces apoptosis in human colon cancer cells."(p.1) [3]

Allium sativum is used to treat a wide variety of diseases in India. The cytotoxic action was in the range 2-50 µg/ml. The consumption of garlic may beneficial providing some kind of protection from cancer. [4]

Garlic intake can modify the risk of colon cancer to women because diallyl disulfide is an effective inhibitor of the growth of neoplastic CMT-13 cells and of N-acetytransferase activity in human colon adenocarcinoma cell line. Furthermore, diallyl disulfide showed to be an effective inhibitor for the promotion phase of 9, 10-dimethyl-1,2- benzanthracene induced skin tumors in the mouse.[5]

In addition to organo-sulphur compounds, eruboside-B, a steroid saponin isolated from garlic bulb, and allixin (phytoalexin), are largely responsible for the anti-carcinogenic activity of garlic. [6]

In an acute and sub-acute toxicity study of *Allium sativum* for determination of LD_{50}, four groups of three rats each were used. The rats were given garlic (*A. sativum*) bulbs extract through oral route at doses of 100, 1000, 2500 and 5000 mg/kg body weight in each group. The extract was administered once and the rats were

observed for death and sign of toxicity within 24 h In the acute toxicity studies, no death was recorded during the treatment period at all doses of the garlic bulb extract administered. The animals were apparently healthy with no sign of toxicity up to the dose of 2500 mg/Kg. However, at 5000 mg/Kg, animals were weak and had intense erthema tachycardia and disorientation but no death was recorded. Thus, LD_{50} was more than 5000 mg/Kg. [7]

As reported in the above acute toxicity studies the oral administration of garlic (A. sativum) bulbs extract did not produce any mortality in mice up to a dose level of 5000 mg/Kg. This may be due to non-toxic therapeutic index of this plant. So the dose of the orodispersible film formulation containing stabilized garlic extract of *Allium sativum* evaluated was very lower that is 2.92 mg/Kg of "Stabilized Garlic Extract" (equivalent to 0.3125 mg/Kg of concentrated garlic extract or 3.75 mg/Kg of orodispersible film), i.e. 1/16000th of the maximum tolerated dose.[8]

Neutraceuticals contains antioxidants which act as free radical scavenger to inhibit over expression of normal oncogenes, or under-expression or disabling of tumour suppressor genes. In the present study, formulation and evaluation of *"In-Vivo" (Colon – 26),* cancer preventive activity is performed.

MATERIALS AND METHODS

Hypromellose (METHOCEL E3 Premium LV) from Dow Chemical Mumbai, Polyvinyl alcohol from S D Fine Chemicals Ltd. Mumbai, .Macrogol 400 from Spectrum Chemicals Mumbai, Mannitol (PEARLITOL 25 C) from Roquettei Active Health Technologies Ltd. Thane, Simethicone Emulsion 30% were obtained from Thurs Organic Pvt. Ltd. Mumbai, Titanium dioxide were purchased from Bimal Pharma Pvt Ltd. Mumbai, Red beet root colour were purchased from Herbo Nutra Delhi India.

All the chemicals and reagents used were analytical grade. The crude garlic cloves was collected from Nanded (MS), India and authenticated by the scientist of the Botanical Survey of India, Pune M. S. India (Certificate No. BSI/WRC/ IDEN.CER./2018/H13-49).

The extraction was done using maceration process with water and alcohol (80:20) as solvent [9, 10] The orodispersible films of garlic were prepared by solvent casting method with water as a solvent. [11-14]

Experimental animals

A total of 24 apparently healthy mice (Murine Tumour Model) with average weight of 20.8± 0.4 gram breaded with human colon cancer cell lines (Colon-26) were procured from National Cancer Institute, Frederick, USA at Anti-cancer drug Screening facility, Advanced Centre for Treatment Research and Education in Cancer (ACTREC), Tata Memorial Centre, Kharghar, Navi Mumbai - 410 208, Maharashtra (CPCSEA Registration Number: 65/GO/ReBiBt/S/99/CPCSEA). The mice were housed in clean plastic cages and maintained under standard laboratory conditions [temperature: 22ºC (± 3ºC); photoperiod: 12 h artificial light and 12 h dark and humidity: 30%–40%]. The mice were maintained on standard animal feeds (Bendel Feeds and Flour Mills, Edo State, Nigeria) and tap water ad libitum. The principles governing the use of laboratory animals as laid out by the CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) and also existing internationally accepted principles for laboratory animal use and care as contained in the OECD (Organisation for Economic Co-operation and Development) guidelines for testing of chemicals were duly observed.

Preparation of animals

The animals were randomly selected, marked to permit individual identification, and kept in their cages for at least 5 days prior to the start of dosing to allow for acclimatisation to the laboratory conditions.

Screening of anti-cancer activity on colon tumour induced mice (Colon – 26): [15, 16, 17]
***In-Vivo* study protocol and sample details:**
Cell line: Colon -26 (BALB/e)
Tumour model: Murine Tumour Model
Sample code: AODF
Route of administration: Oral
Dose: 3.75 mg/Mice (Dilute concentrated sample in sufficient quantity of water to feed to mice)
Dosing frequency: Daily dosing for 30 Days at morning and evening
Duration of study: 30 Days
No. of mice for test sample: 6 Mice
No. of mice as control: 6 Mice
No. of mice as positive control: 6 Mice

Study no. 401
Tumor: Colon-26
Transplant date: 10/2/2017
Experiment started date: 16/2/2017
Experiment ended: 17/3/2017
Treatment
Group A: Control Group: Normal saline (0.2 mL/mouse)
Group B: Positive Control Group (ADR - Adriamycin): 2.5mg/Kg I.P. injection on day 1, 5, 9
Group C: Test Group (AODF – Garlic orodispersible film): 3.75mg/mice oral twice a day x 30 days
Group D: Test + Positive Control Group: (ADR + AODF - Half dose of Adriamycin + Half dose of garlic orodispersible film).

Ethical approval

Permission to carry out this work and ethical clearance were obtained from the Institutional Review Board (IRB) of the Advanced Centre for Treatment Research and Education in Cancer (ACTREC), Tata Memorial Centre, Kharghar, Navi Mumbai - 410 208, Maharashtra.

RESULTS AND DISCUSSION

On day 30, the longest and shortest diameters of tumors were measured with a digital caliper and the most accurate volume calculations were obtained using the formula Tumor volume (V) in cc,

$$V = (L \times W^2)/2$$

Where,
L= Longest diameters of tumor
W= Shortest diameters of tumor
The tumor volume at day n is expressed as Relative Tumor Volume (RTV) and calculated according to the following formula: $RTV = TVn/TV_0$, where TVn is the tumor volume at day n and TV_0 is the tumor volume at day 0.
The T/C% is determined by calculating RTV as T/C% = mean RTV of treated group / mean RTV of control group x 100.

Table 1: Relative Tumor Volume of mice with time

Weeks	Days	Relative Tumor Volume (RTV*)			
		Group A	Group B	Group C	Group D
0.00	0	1.00	1.00	1.00	1.00
0.71	5	5.55	2.59	4.13	4.20
1.29	9	14.81	10.55	15.64	12.36
1.71	12	27.71	15.36	31.63	21.25
2.14	15	43.11	25.67	35.09	31.95
2.57	18	58.93	35.67	55.02	43.98
3.00	21	62.56	48.73	69.72	47.64
3.57	25	79.18	55.32	82.52	55.86
4.29	30	97.90	63.93	85.31	68.70

* RTV = Relative Tumor Volume = Tumor Volume on day of measurement/ Tumor Volume on day 1

Table 2: Percent inhibition of tumor

Groups	Group B	Group C	Group D
Percent inhibition of tumor	32.60	10.75	27.72

Table 3: T/C values from RTV data

T/C, From RTV data				
Weeks	Days	Group B	Group C	Group D
0.00	1	1.00	1.00	1.00
0.71	5	0.47	0.74	0.76
1.29	9	0.71	1.06	0.83
1.71	12	0.55	1.14	0.77
2.14	15	0.60	0.81	0.74
2.57	18	0.61	0.93	0.75
3.00	21	0.78	1.11	0.76
3.57	25	0.70	1.04	0.71
4.29	30	0.65	0.87	0.70

Table 4: % Survival in all four treated groups viz., Group A (Control - Normal saline 0.2 mL/mice), Group B (Positive Control - Adriamycin 2.5mg/Kg I.P. injection on day 1, 5, 9), Group C (Garlic orodisperssible film - 3.75mg/mice oral twice a day x 30 days), Group D (Half dose of Adriamycin + Half dose of garlic orodisperssible film)

% Survival					
Weeks	Days	Group A	Group B	Group C	Group D
0.00	1	100	100	100	100
0.71	5	100	100	100	100
1.29	9	100	100	100	100
1.71	12	100	100	100	100
2.14	15	100	100	100	100
2.57	18	100	100	100	100
3.00	21	100	100	100	100
3.57	25	100	100	100	100
4.29	30	100	100	100	100

Table 5: Animal body weight (grams) during study period

Average animal body weight (grams) data					
Weeks	Days	Group A	Group B	Group C	Group D
0.0	1	21.4	20.4	20.8	20.6
0.7	5	21.8	19.9	20.8	19.8
1.3	9	19.1	19.0	20.6	20.3
1.7	12	19.1	17.4	19.1	17.7
2.1	15	19.3	16.4	17.9	16.9
2.6	18	18.3	14.0	17.3	16.9
3.0	21	18.9	17.4	17.6	17.0
3.6	25	19.4	17.5	18.1	17.4
4.3	30	19.4	17.7	18.4	17.7
Average animal body weight loss (grams) after 30 days		2.0	2.7	2.4	2.9

Table 6: Tumor volume of Group A, Group B, Group C, and Group D

Week	Days	Tumor volume - Group A						Tumor volume - Group B					
		Mouse 1	Mouse 2	Mouse 3	Mouse 4	Mouse 5	Mouse 6	Mouse 1	Mouse 2	Mouse 3	Mouse 4	Mouse 5	Mouse 6
0.00	1	0.05	0.06	0.05	0.05	0.06	0.07	0.05	0.07	0.06	0.04	0.04	0.06
0.71	5	0.30	0.21	0.23	0.27	0.44	0.50	0.14	0.09	0.14	0.15	0.14	0.11
1.29	9	0.96	0.55	0.64	0.71	1.39	0.87	0.57	0.50	0.44	0.41	0.51	0.78
1.71	12	1.64	1.06	1.25	1.35	2.85	1.43	0.76	0.68	0.77	0.74	0.73	1.00
2.14	15	3.12	1.44	1.56	2.44	3.20	3.20	0.83	1.29	1.27	1.01	1.97	1.31
2.57	18	4.68	1.90	1.90	2.73	4.64	4.66	1.20	1.65	1.95	1.34	2.83	1.66
3.00	21	4.41	1.96	2.25	3.07	4.86	5.26	1.32	1.89	2.81	1.86	3.70	3.06
3.57	25	5.35	2.57	3.22	3.86	5.90	6.67	1.57	2.17	3.33	2.14	4.06	3.40
4.29	30	6.21	3.97	4.21	5.10	6.73	7.86	2.02	2.88	3.75	2.48	4.39	3.86
Week	**Days**	**Tumor volume - Group C**						**Tumor volume - Group D**					
		Mouse 1	Mouse 2	Mouse 3	Mouse 4	Mouse 5	Mouse 6	Mouse 1	Mouse 2	Mouse 3	Mouse 4	Mouse 5	Mouse 6
0.00	1	0.03	0.04	0.03	0.07	0.04	0.05	0.05	0.04	0.05	0.06	0.05	0.04
0.71	5	0.19	0.14	0.18	0.25	0.10	0.19	0.24	0.23	0.11	0.29	0.20	0.13
1.29	9	0.48	0.35	1.18	0.93	0.40	0.59	0.48	0.54	0.60	0.96	0.54	0.48
1.71	12	1.38	1.07	1.71	1.49	0.91	1.21	0.81	1.21	1.16	1.10	0.83	0.93
2.14	15	1.31	1.49	1.88	1.69	0.97	1.29	1.10	1.87	1.82	1.66	1.15	1.47
2.57	18	1.70	1.93	3.73	2.62	1.76	1.70	1.23	2.15	2.73	2.38	1.72	2.34
3.00	21	2.47	2.61	4.42	3.10	2.11	2.22	1.28	2.21	2.82	2.85	1.90	2.59
3.57	25	2.83	3.10	5.19	3.54	2.51	2.91	1.50	2.79	3.09	3.30	2.28	3.00
4.29	30	3.58	3.59	5.54	4.45	3.37	3.53	2.11	3.43	3.77	4.19	2.59	3.57

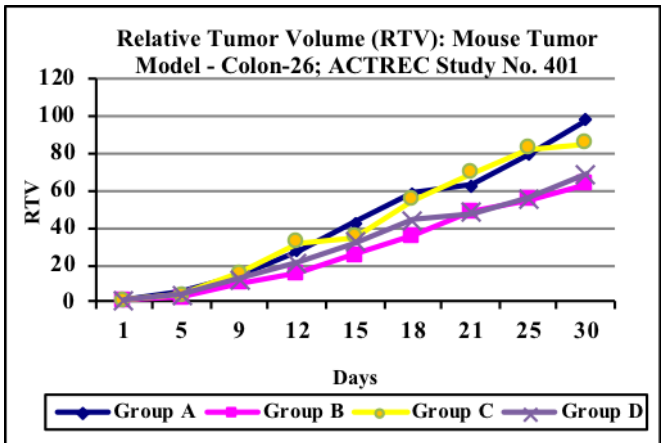

Figure 1: Relative Tumor Volume of mice with time

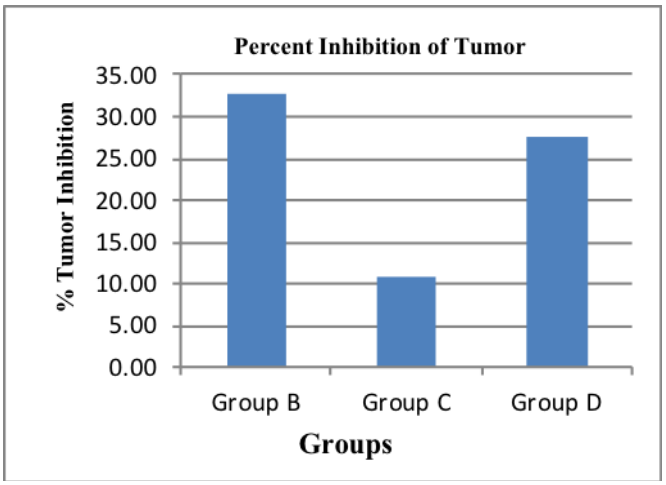

Figure 2: Percent Inhibition of tumor for Group B, Group C and Group D

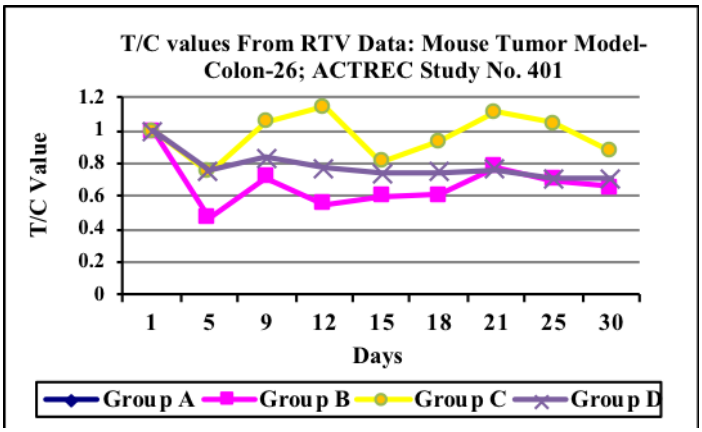

Figure 3: Plot of T/C values versus time (days) from RTV data

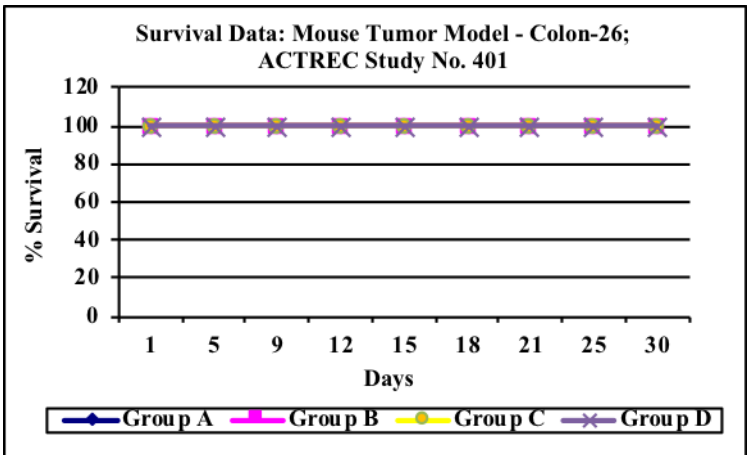

Figure 4: Plot of percentage of mice survival in group A, B, C, and D versus time (Days)

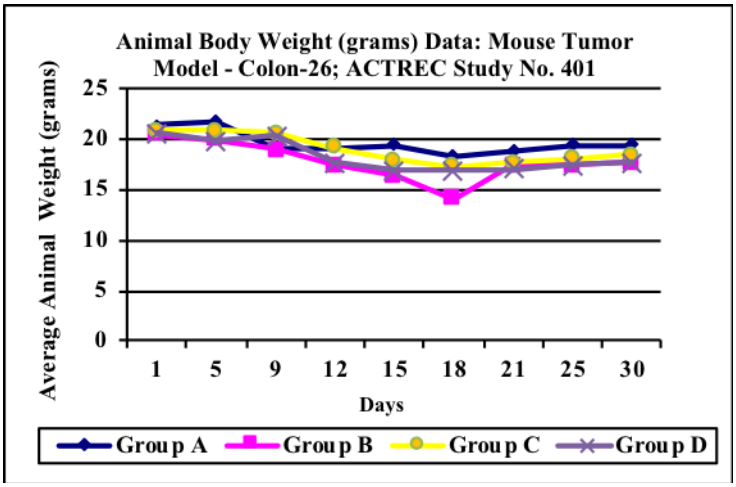

Figure 5: Plot of Average Animal Body Weight (Grams) versus time (Days)

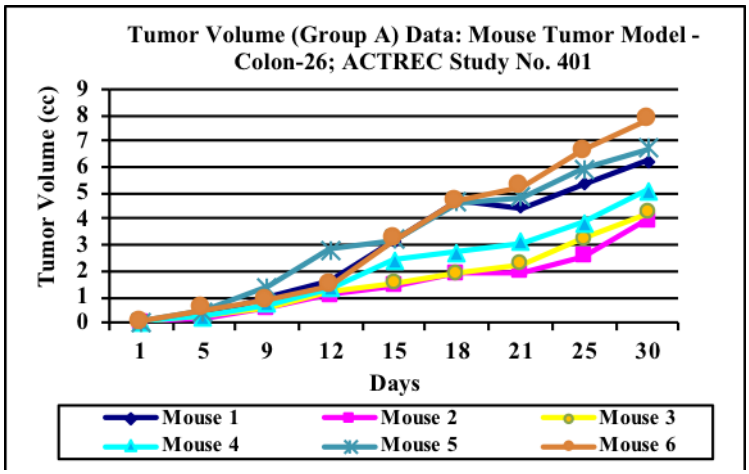

Figure 6: Tumor volume (cc) of individual mice of Group A

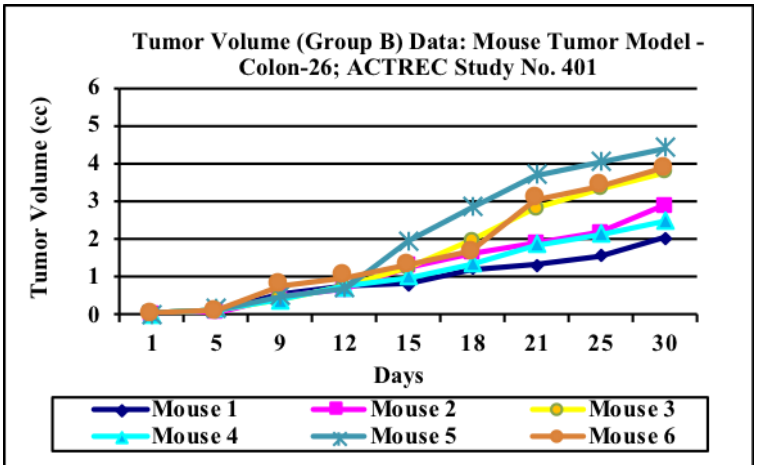

Figure 7: Tumor volume (cc) of individual mice of Group B

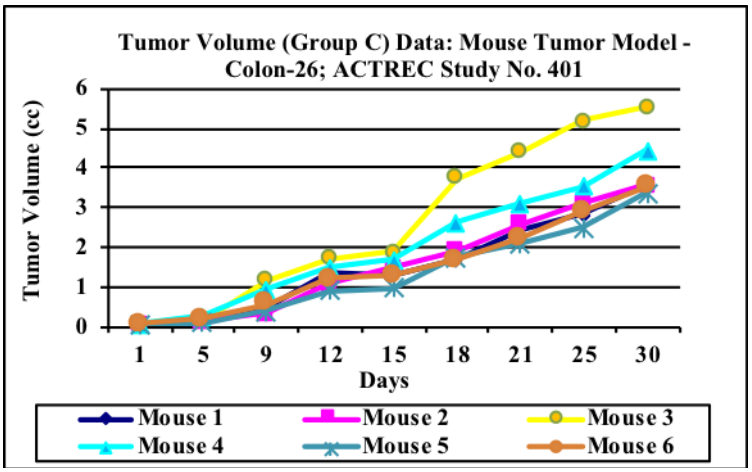

Figure 8: Tumor volume (cc) of individual mice of Group C

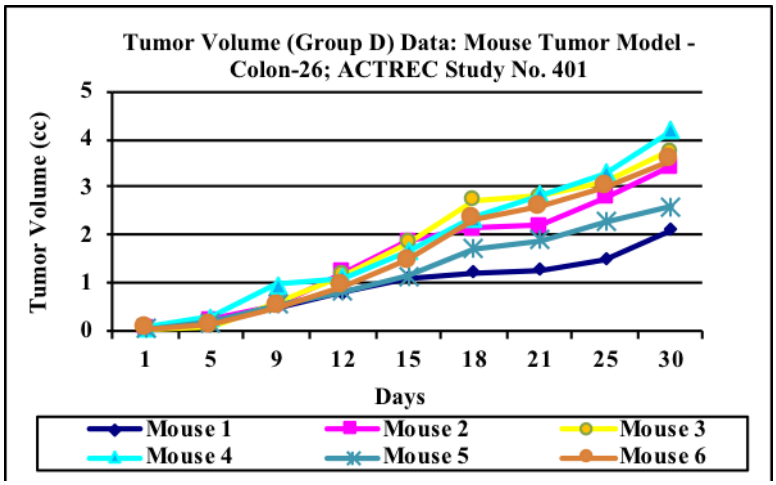

Figure 9: Tumor volume (cc) of individual mice of Group D

Percent inhibition of tumor

Average tumor volume of control mice −Average tumor volume of treated mice/Average tumor volume of control mice × 100.

As per data of relative tumor volume of mice with time presented in table 1 and represented by figure 1, relative tumor volume for Group A, Group B, Group C and Group D was 97.90, 63.93, 85.31, 68.70 respectively. Highest tumor volume observed in Group A, Control Group fed with Normal saline (0.2 mL/mouse) i.e. 97.90 mm^3 and lowest tumor volume 63.93 mm^3observed in Group B, Positive Control Group receiving reference anticancer drug Adriamycin 2.5mg/Kg I.P. injection on day 1, 5, 9. While relative tumor volume for Group B 85.31, receiving garlic orodispersible film 3.75mg/mice oral twice a day for 30 days shows comparable reduction in tumor volume as that of reference anticancer drug of allopathic origin. Also the results for Group D (Test + Positive Control Group) 68.70, receiving half dose of reference anticancer drug Adriamycin and half dose test formulation, garlic orodispersible film shows complete synergism with reference anticancer drug Adriamycin.

Almost no tumor growth inhibition in Group A and comparatively significant tumor volume reduction in Group B, Group C and Group D show that reference anticancer drug Adriamycin, garlic orodispersible film and half dose of reference anticancer drug Adriamycin and half dose test formulation, garlic orodispersible film is effective to reduce tumor growth in dose dependent manner.

As shown in table 2 and represented by figure 2, it was observed that percent inhibition of tumor was 10.75% for the Test Group C (AODF) which is comparable to percent inhibition of tumor in Positive Control Group B (ADR) i.e. 32.60%. Also the results for percent inhibition of tumor in Group D (Test + Positive Control Group: AODF+ADR), 27.72% lies well in within Group B and Group C indicating synergistic action of garlic orodispersible film.

As shown in table 3 and represented by figure 3, it was observed that T/C values for Group B, Group C and Group D on day 30 were 0.65, 0.87 and 0.70 respectively. T/C values were least for Group B and higher for Group C. While. T/C values for Group D lies well in between Group B and Group C indicating synergistic action of garlic orodispersible film.

As shown in table 4 and represented by figure 4, there is 100% survival rate of mice for all four treated groups viz., Group A (Control - Normal saline 0.2 mL/mice), Group B (Positive Control - Adriamycin 2.5mg/Kg I.P. injection on day 1, 5, 9), Group C (Garlic orodispersible film - 3.75mg/mice oral twice a day x 30 days), Group D (Half dose of Adriamycin + Half dose of garlic orodispersible film).

As shown in table 5 and represented by figure 5, all animals of group A, B, C, and D show weight loss less than 4 grams/ mouse.

Toxicity criteria: Mortality and weight loss ≥4 grams/ mouse are considered to indicate toxicity.
Hence from the data shown in table 4 and table 5 it was observed that all the three given doses, Adriamycin: 2.5mg/Kg I.P. injection on day 1, 5, 9, Garlic orodispersible film: 3.75mg/mice oral twice a day x 30 days and Half dose of Adriamycin + Half dose of Garlic orodispersible film in Group B, Group C and Group D respectively were non-toxic to animals.

Tumor volume of individual mice of each group is shown in Table 6 and tumor volume (cc) versus time (Days) is represented in figure 6, 7, 8 and 9.

CONCLUSION

The findings of the present study suggest that orodispersible film formulation containing stabilized garlic extract of *Allium sativum* Linn. possesses promising tumor inhibition properties for colon cancer in mice **(**Colon – 26), which was evident by the decreased growth of cancer cells by test sample versus growth of cancer cells in control condition. As there were no evidences of mortality or weight loss, the product is found to be non-toxic. Hence to warrant further extensive studies are necessary to confirm antitumor properties of *Allium sativum* Linn. bulbs in human beings to determine the precise mechanism$_{(s)}$ of action safety, efficacy, pharmacokinetic and pharmaco-dynamics and to identify, isolate, characterize the specific bioactive molecules responsible for the observed antitumor activity. The present study was carried out to explore anticancer potential of orodispersible film formulation containing stabilized garlic extract of *Allium sativum* Linn. in colon tumour induced mice **(**Colon – 26).

Garlic orodispersible film formulation could be a future's dosage to prevent occurrence and relapse of colon cancer as well as treatment of colon cancer.

These results suggest that presumably stabilized garlic extract in orodispersible film formulation protects normal cells to convert into tumor cells in mice.

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