

Lack of the Beneficial Effects of Mirazid (*Commiphora molmol*) When administered with Chemotherapeutic Agents on Ehrlich Ascetic Carcinoma Bearing Mice

Sabry A. EL-Naggar

Department of Biology Faculty of Science, Al-Jouf University, KSA

Abstract: Recently, the complementary and alternative medicines are used all over the world to enhance the anti-tumor activity and to ameliorate the side effects after chemotherapy treatments. The current study was conducted to assess the efficacy of oleo-gum-resin of *Commiphora molmol* (Family: Burceraceae) known as Myrrh and the commercial extract known as Mirazid (MRZ) as anti-tumor agents and its possible role as a complementary medicine with the standard chemotherapeutic drugs; cisplatin or 5-Fluorouracil (5-FU). Ehrlich ascetic carcinoma (EAC) cells (2×10^6 cells / mouse) were inoculated in eighty four female Swiss albino mice by intraperitoneal (i.p.) injection. After 24 hours of tumor inoculation, mice were divided into seven groups (n=12). MRZ was injected alone or in combination with cisplatin or with 5-FU daily for 6 days. The anti-tumor efficacy was evaluated by using median survival time (MST), tumor ascetic volume, counting the viable and non-viable tumor cells. Some biochemical parameters and the hematological profile were assessed as well. Analyzing data showed that the median lethal dose LD50 and LD90 of MRZ to normal mice were 1739.5 and 2777 mg/kg, respectively. The study showed that the metronomic provision of MRZ (100 mg/Kg/6 days daily or 250 mg/Kg every other day for 6 days) alone had no anti-tumor activity against EAC *in vivo*. In addition, the treatment with MRZ alone or in concomitant with cisplatin or 5-FU didn't change the hematological profile, but it did some biochemical changes. Collectively, the treatment with MRZ had no effect as anti-tumor agent and didn't show any beneficial effects when administered in concomitant with chemotherapeutic agents.

Key words: Ehrlich ascetic carcinoma (EAC) • Mirazid • *Commiphora molmol* • Cisplatin • 5-FU • Anti-tumor • Efficacy

INTRODUCTION

Cancer represents the largest cause of death all over the world and threaten over 6 million lives every year. Ten million new cases of cancer are diagnosed globally every year [1]. Despite the progress using surgical removal, chemotherapy and/or radiotherapy, the outcomes are still of limited. This limitation is due to the tumor cell resistance or due to the escape from the immune system. In addition, most of the existing anti-tumor drugs showed some sort of side effects such as, paclitaxel [2], doxorubicin [3, 4] and cyclophosphamide [5]. For these reasons, recent studies were conducted to find new modalities to minimize the side effects after treatment with the chemotherapeutic agents [5-8]. One of these modalities is to utilize the medicinal herbs as complementary and alternative medicines to reduce the side effects and/or to enhance the chemo-sensitivity of the applied drugs [8-10]. Furthermore, it has been reported

that some traditional plants were tested as anti-cancer agent. Curcumin and ginger have found to be a potent anticancer efficacy *in vivo* and *in vitro* [11-13]. Furthermore, it has reported that gallic acid which extracted from garlic seeds can restrain the BEL-7404 cells proliferation and induce apoptosis *in vitro* [14].

In a recent study, the treatment with *Commiphora molmol* (myrrh) which known commercially under the name of Mirazid (MZR) in the Egyptian pharmacies showed insignificant activity against fascioliasis [15, 16]. Also, it has reported that myrrh had hypocholesteremic, antipyretic, antihistaminic, anti-gastric ulcer [17-19]. In Egypt, several studies have been conducted to evaluate the anti-schistosomal efficacy of myrrh [20], anti-fascioliasis [21]. The present study was carried out to evaluate the antitumor activity of myrrh (Mirazid) using Ehrlich ascites carcinoma (EAC) in Swiss albino mice and to evaluate its role when administered in concomitant with cisplatin or 5-FU using EAC-model.

MATERIALS AND METHODS

Tumor Cell Line: Ehrlich ascites carcinoma (EAC) cells were originally obtained from the National Cancer Institute (Cairo University, Egypt). The tumor line was maintained in female mice and has been propagated in our laboratory by weekly intra-peritoneal (i.p) inoculation of about 2×10^6 cells/ mouse. The tumor cells multiplied relatively freely within the peritoneal cavity. Unless otherwise indicated, the EAC cells were obtained from donor mice on the eight day of tumor growth. The cells were withdrawn by sterile disposable syringe and diluted with physiological saline. The viability of the cells was 97% as judged by trypan blue exclusion assay and counted with haemocytometer.

Animals: Adult Swiss female albino mice weighting 20 ± 2 g were used and obtained from Teodor Bilharis institute (TBI), Imbaba, Giza, Cairo, Egypt). Animals were kept in clean and dry plastic cages, as 6 animals per cage in 12h/12h dark/light cycle under normal laboratory condition of temperature and humidity, fed with rodent pellets and tap water ad libitum.

Chemical Compounds: Cisplatin and 5-FU were obtained from a local pharmacy and prepared under the sterile conditions and kept at 4°C until used. MRZ was obtained from a local pharmacy and prepared freshly before the treatment; mice were treated with 2mg/kg of cisplatin (i.p) or treated with 20mg/kg of 5-FU for six consecutive days. MRZ was injected (i.p) as 100 mg/kg for six consecutive days alone or in combination with cisplatin or with 5-FU.

Experimental Protocol:

- Sixty female Swiss albino mice were divided into 4 groups (n=15) and injected with different doses of MRZ orally (Table 1) and left for 24 hrs after injection to determine the lethal dose which killed 50 percent of normal female mice.
- Eighty four female Swiss albino mice were divided into 7 groups of 12 animals each, as follows: group I (naive mice); group II EAC-bearing mice (positive controls); group III: EAC-bearing mice treated with cisplatin (2mg/kg) i.p; group IV: EAC bearing mice treated with MRZ i.p (100 mg/kg/day); group V: EAC-bearing mice treated with a concomitant doses of cisplatin and with MRZ i.p.; group VI: EAC bearing mice treated with 5-FU (20mg/kg) i.p ; group VII: EAC bearing mice treated with 5-FU (20mg/kg), i.p and

MRZ i.p. After 24 hours of inoculation, mice were delivered the doses for six consecutive days. On the day +14, fifty percent (50%) of mice were sacrificed, blood samples were collected from all groups and the plasma quickly separated and frozen at -20 C until used. The anti-tumor activity was measured in EAC bearing mice with respect to the following parameters; the changes in the total body weight; tumor volume; total tumor cell counts. In brief, mice were dissected and the ascitic fluid was collected from the peritoneal cavity and the volume of the fluid was measured by taking it in a graduated centrifuge tube. To count the tumor cells, the ascitic fluid was diluted 1:10-1:15 and the cells were counted by staining with trypan blue.

Estimation of Biochemical Parameters: After the collection of blood samples, mice were sacrificed and their liver were excised, rinsed in ice-cold normal saline, blotted dry and weighed. A 10% w/v homogenate was prepared in normal saline. The homogenate was centrifuged at 4000 rpm for 10 min at 4°C. The supernatant thus obtained was used for the estimation of transaminases (AST and ALT), alkaline phosphatase (ALP). Blood samples from all groups were centrifuged and the sera were collected to estimate urea and creatinine as indication for the kidney functions.

Hematological Studies: Red blood cells (RBCs), packed cell volume (PCV), hemoglobin content (Hb g/dl) and white blood cell (WBCs) counts were measured from freshly blood samples obtained from the orbital plexus of the eyes of all groups under the study using the electronic blood counter. Differential WBC was carried out from blood smears of normal, untreated and treated groups.

Statistic al Analysis: All values were expressed as mean \pm SD. Statistical analysis was performed by student's 't' test P values <0.05 were considered as significant when compared to control.

RESULTS

Lethal Dose Value of Mirazid in Normal Female Mice: As shown in table 1, the effect of different doses of MRZ when administered as a single oral dose to normal female mice was assessed. The mortality data were recorded 24 hours post MRZ administration. Analyzing data showed that the median lethal dose LD50 and LD90 of MRZ to normal mice were 1739.5 and 2777 mg/kg, respectively.

Table 1 Mortality rate of naïve mice injected with different doses of Mirazid

Dose mg/kg	No. of mice		% Death
	Tested	Killed	
1000	15	2	13
1500	15	5	33
2000	15	9	60
2500	15	11	73

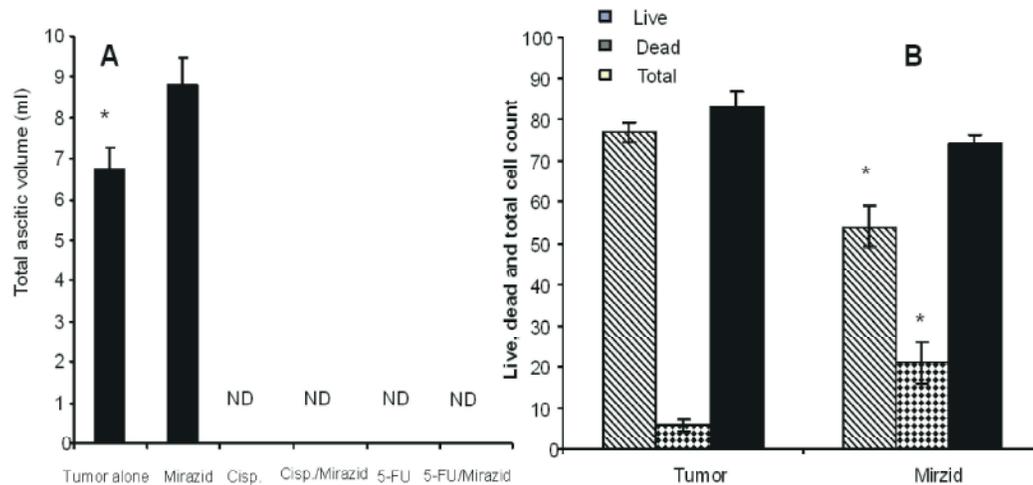


Fig. 1: Shows the total ascitic volume and the total tumor cell counts after 14 days post inoculation of EAC-cells. Different groups of mice (12 per group) were inoculated with 2×10^6 EAC-cells, 24 hours later, mice were treated according to the experimental plan. A) All groups were sacrificed on day 14 and the total ascitic volume were measured using graduated tubes B). The total tumor cell count, viable and dead cells were determined using trypan blue stain.

The true values of the LD50 and LD90 may be expected to lie between (1606.7– 1883.3) and (2487.9 – 3066.1) mg/kg, respectively.

Treatment with Mrz Didn't Show Antitumor Effect Against EAC *in vivo*: After 24 hrs of EAC inoculation, mice were treated with MRZ alone or in combination with cisplatin or with 5-FU. The results showed that both of the untreated group and MRZ treated mice had tumor where the ascetic tumor volume in untreated and MRZ treated mice were 6.75 ± 0.5 and 8.8 ± 0.7 , respectively (Fig. 1A). While the groups treated with cisplatin, cisplatin/ MRZ, 5-FU or 5-FU/mirazid had no tumor after 14 days of inoculation. Interestingly, the treatment with MRZ and cisplatin together showed a toxic effect on the tumor bearing mice, whereas 5 mice of 12 were dead starting from day 4 until day 12 (data not shown). The results showed that although the total ascetic volume in the group treated with MRZ was slightly higher than the volume of the untreated group, the total number of live cells was less than it in the untreated group. Furthermore, the results showed that the total number of dead cells in the MRZ

treated group was significantly increased than the number of the untreated group (Fig. 1B).

Treatment with Cisplatin and MRZ Decrease the Loss of Body Weight: As shown in figure 2, as compared to the untreated group, the treatment with cisplatin alone showed a significant decrease in the total body weight. The combinatorial treatment with cisplatin and MRZ showed a marginal increase in the total body weight when compared to the group treated with cisplatin alone (Fig. 2). Interestingly, the treatment with 5-FU alone or with MRZ showed no changes in the body weight as compared with the untreated group. Both of untreated and MRZ treated groups showed increased in the total body weight at the day 14 after tumor inoculation due the increase of the total ascetic volume.

Treatment with MRZ Increased the Median Survival Time (MST): Half numbers of mice were left under the laboratory condition to calculate the median survival time (MST). The results showed that the untreated group was died 27 days post inoculation while treated group with

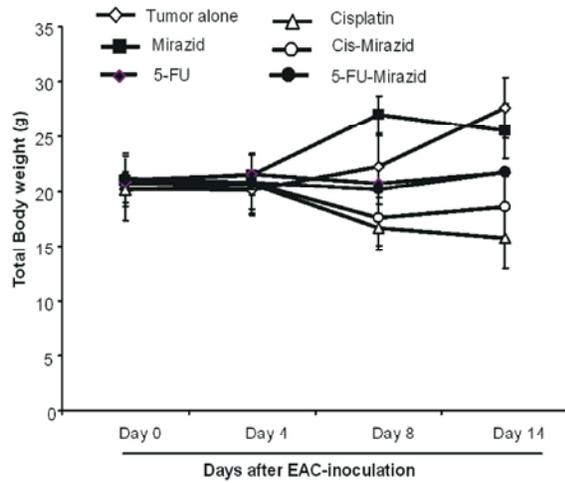


Fig. 2: Shows the kinetic changes in the total body weight after 14 days post inoculation of EAC-cells. Different groups of mice (12 per group) were inoculated with 2×10^6 EAC-cells, 24 hours later, mice were treated according to the experimental plan. Mice were weighted on day 0, 4, 8 and 14 after inoculation with tumor. The tumored groups were sacrificed on day 14 and the changes in the total body weight were calculated.

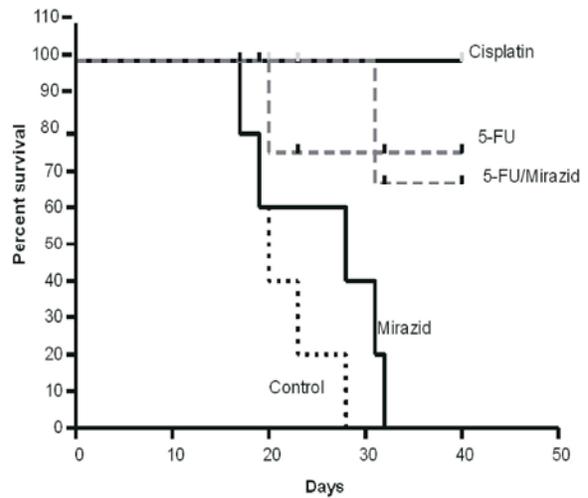


Fig. 3: Treatment with Mirazid for 6 days daily showed no significant changes in the MST as compared with the untreated group. Different groups of mice were inoculated with 2×10^6 EAC-cells, 24 hours later, mice were treated daily for 6 days according to the experimental protocol. Fifty percent of all mice were housed after 14 days post inoculation and the mortality rate was observed daily to determine the MST.

Table 2: Shows some biochemical parameters for the liver and kidney of all groups under the study

Groups	Liver functions (homogenate 1%)			Kidney functions (Serum)	
	AST	ALT	ALP	Creatinine	Urea
Cont. (Naive)	65±5.5	55±4.5	18±2.5	0.8±0.15	20±2.5
Untreated	71.5±23	79±3.0	25±4.5	0.7±0.2	30±3.5
Cisplatin	54±16.8	89±5.5	19±3.0	1.7±0.3*	67±9.0*
Mirazid	91±1.8*	82±6.2	34±5.2*	1.7±0.11*	69±7.0*
Cis/ Mirazid	55±24.5	81±3.0	35±4.0*	1.2±0.11*	88±7.5*
5-FU	65±27.7	77±1.2	11±4.0	1.4±0.11*	51±1.4*
5-FU/ Mirazid	51±27*	79±3.0	25±9.9	1.4±0.2*	41±10

* Differences are statistically significant from the control group at $p < 0.05$.

Table 3: Shows the hematological profile of all groups under the study

Groups	Hematological profile (Mean±SD)				Differential leucocytes		
	RBCs $\times 10^6$ /ul	Hb (g/dl)	Hct (%)	WBCs $\times 10^3$ /ul	Neut. (%)	Lymph. (%)	Mono. (%)
Control (naive)	9.5±0.3	13.5±0.7	43±2.8	10.5±0.5	6.5±1.5	75±9.0	17±6.0
Untreated	7.7±1.2	11.5±1.5	35±5.0	17.5±0.77	8.5±0.7	50.5±6.3	37.5±2
Cisplatin	9±0.5	15±0.8	45±2.8	9±1.8	10.5±0.7	57±10.0	19.5±5.0*
Mirazid	7.5±0.9	11.5±1.5	33.5±4.5	23±0.6*	17±0.6*	45.5±7.5	37.5±3.5
Cisp/Mirazid	8.8±1.4	14±2.0	42±6.0	12±1.3	5.5±0.7	68.6±5.6	23±3.6
5-FU	9±0.8	13.5±1.2	40.5±3.8	18±0.2	6±1.0	75.5±6.3	18.5±5.2*
5-FU/Mirazid	9±0.9	15±1.0	40.5±2.0	13.5±1.0	4±1.2	79±6.0	17±4.3*

* Differences are statistically significant from the control group at $p < 0.05$.

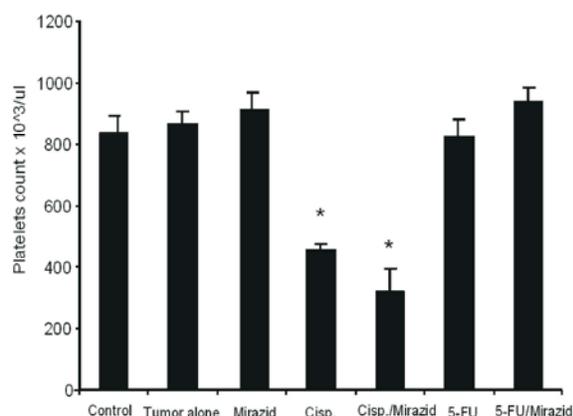


Fig. 4: Cisplatin injection led to a significant reduction in the number of platelets after 14 days post inoculation of EAC-cells. Different groups of mice were inoculated with 2×10^6 EAC-cells, 24 hours later, mice were treated according to the experimental plan. In day 14 post inoculation, all groups of mice were bled using the retro-orbital bleeding technique, blood samples were transferred into tubes with anti-coagulant and samples were analyzed to estimate the platelets count

MRZ was died 5 days after the untreated group (Fig. 3). The results showed also that the treatment with cisplatin or 5-FU or with a combination of MRZ and cisplatin or 5-FU and MRZ led to cure the mice after 14 days of tumor inoculation. Interestingly, the recurrence of tumor appeared only on the group treated with 5-FU/mirazid after 40 days from the beginning of the experiment (data not shown).

Effect of MRZ Injection on Some Biochemical Parameters on EAC-Bearing Mice: The results showed that as compared with naïve mice, AST enzyme was increased in the untreated group (tumor alone). Treatment with cisplatin, cisplatin/MRZ, 5-FU or 5-FU/mirazid return the level of this enzyme into the normal range, in contrast the treatment with MRZ alone significantly increased the level of AST enzyme above the normal value. All groups showed increase in the level of ALT as compared to the naïve mice (Table 1). Also, as compared to naïve mice, the untreated group of mice showed an increase in the level of alkaline phosphatase (ALP). The treatment with cisplatin or 5-FU showed similar levels of ALP when compared to naïve mice. Treatment with MRZ and cisplatin or with 5-FU increased the level of ALP in the

liver tissues (Table 2). As compared with the untreated group, the level of creatinine and urea were increased in all the treated groups.

Treatment with MRZ Altered the Hematological Profile: The results showed that the treatment with MRZ had no effect on the total RBCs count, Hb concentration or the packed cell volume (PCV) when compared with the untreated group (Table 2). In contrast, the treatment with MRZ alone led to a significant increase in the total number of white blood cells, especially in the percentage of neutrophil cells. Interestingly, treatment with cisplatin or 5-FU alone or in combination with MRZ returns the hematological profile into the normal value as compared with the normal naïve mice (Table 3). Treatment with cisplatin alone or cisplatin and MRZ showed a dramatic change in the total number of platelets as compared with the untreated and control naïve mice (Fig. 4).

DISCUSSION

Some recent studies showed that Mirazid (*Commiphora molmol*) has potent anti-tumor activity against different tumor cell lines [22]. In this study, the role of MRZ as anti-tumor drug and its role as complementary medicine during the treatment with chemotherapeutic agents were assessed. Our results showed that the treatment with MRZ alone as compared with the reference drugs; cisplatin and 5-FU had no any anti-tumor activity when administered for 6 consecutive days at dose of 100 mg/kg. Our results weren't in agreement with the previous study that showed MRZ has anti-tumor activity [22, 23]. After the treatment with MRZ alone, all mice died soon after the control group directly and these results indicated that MRZ had no any anti-tumor effect under these treatment doses. Interestingly, despite of the total ascetic volume obtained from the MRZ treated group was higher than this volume of the untreated group, the number of the dead tumor cells was higher in the group treated MRZ than this number of the untreated group. Furthermore, the number of the live cells was lower in the MRZ treated group as compared with the untreated group.

This observation may indicate that the treatment with MRZ with 600 mg/kg in metronomic dose showed some toxic effect on the Ehrlich carcinoma cells but not enough to stop the progression of the EAC-cells, this result was not in agreement with the previous study by Nomicos [22] which showed that MRZ has a potent antitumor activity. The treatment with cisplatin alone led to sever loss in the

total body weight after 14 days post-inoculation of tumor and this could be due to the toxicity of the cisplatin. Even though, the treatment with cisplatin and MRZ showed toxic effect [24], the concomitant treatment marginally increased the total body weight of mice. Interestingly, the treatment with 5-FU alone or in combination with MRZ had no significant changes in the total body weight. Surprisingly, mice were treated with 5-FU and MRZ together showed recurrence of the tumor after 40 days of the beginning of the experiment. This result could explain that MRZ may be interfere with the action of the 5-FU on Ehrlich carcinoma cells *in vivo*.

It is well known that liver dysfunctions and the hepato-cellular damage caused by toxic agents are associated by the significant increase in ALP and GPT levels. Treatment with a combination of cisplatin and MRZ increased the level of ALP and urea in the liver tissue and in serum of the blood and this could be explain why the provision of MRZ was toxic when injected with cisplatin. Furthermore, the growth of the tumor in the experimental animals is known to be associated with decrease RBC count, Hb content and increase in leukocytes and platelets and the reversal of lymphoid-myeloid ratio in the differential WBC count [25]. As compared with the naïve mice, the treatment with cisplatin alone, cisplatin/ MRZ, 5-FU or 5-FU/ MRZ return the hematological parameters into the normal values. In contrast, the untreated group and the MRZ treated group showed decrease in some hematological parameters such as RBC count, HCT, Hb content. Treatment with MRZ only increased the total WBCs and neutrophils as compared with the untreated groups. Again the treatment with cisplatin or with a combination of cisplatin and MRZ showed a significant reduction in the number of the circulated platelets and this could be explaining the cisplatin toxicity in the hematological level and this reduction is due to the direct toxic effect of cisplatin [24]. In conclusion, the treatment with MRZ against Ehrlich ascetic carcinoma bearing mice showed no effect. In addition, the concomitant administration of MRZ with cisplatin was toxic and cause recurrence and grow of the tumor again when injected concomitantly with 5-FU.

CONCLUSION

Given that, the treatment with MRZ is not recommended as complementary drug for patient under the treatment with chemotherapeutic agents due to the lack beneficial effect as anti-tumor or complimentary medicine.

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