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The protective effects of methyl jasmonate against adriamycin – induced hepatic and renal toxicities

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Abstract

The aim of the study was to investigate the protective effect of methyl jasmonate (MJ) in adriamycin (ADR) induced hepatic and renal toxicities. 36 BALB/c mice were randomly divided into control, ADR (20mg/kg), MJ (50mg/kg) only, MJ (100mg/kg) only, MJ (50 mg/kg) + ADR, MJ (100 mg/kg) + ADR groups (n = 6). The 2 doses of MJ was administered for 7 days in MJ only groups, ADR was administered intraperitoneally on the 8th day after pretreatment with the 2 different doses of MJ while ADR was administered on the 8th day only for the ADR only group. The malondialdehyde (MDA), glutathione (GSH), H_2O_2 generation, superoxide dismutase (SOD), catalase (CAT), glutathione S-transferase (GST), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea and creatinine in the liver, kidneys and serum samples as applicable were estimated. Tissue MDA, H_2O_2 generation, and GST activity were markedly elevated while GSH content, CAT and SOD activities were significantly reduced in the tissues when compared to the control ($p < 0.05$). Pretreatment with MJ ameliorated ADR toxicities, with a significant reduction in serum urea concentration, ALT activity, MDA level, H_2O_2 generation, GST activity and a significant elevation in GSH content, CAT and SOD activities in the organ tissues. MJ induced significant reduction in MDA level and increase of GSH content in liver and kidney tissues. This study suggests that MJ may play an overall protective effect on ADR–induced toxicities in liver and kidneys and the inhibition of tissue peroxidative damage might contribute to this beneficial effect.

Keywords: *Oxidative stress, adriamycin, methyl jasmonate, tissue peroxidative damage*

Résumé

Le but de cette étude était d'évaluer l'effet protecteur de méthyle jasmonate (MJ) dans les toxicités rénales et hépatiques induite par l'adriamycine (ADR). Trente six (36) souris BALB / c ont été groupés au hasard à savoir groupe pilote, groupe ADR (20mg/kg), groupe MJ (50mg/kg) uniquement, groupe MJ (100mg/kg) uniquement, groupes MJ (50 mg / kg) + ADR, groupe MJ (100 mg / kg) + ADR (n = 6). Les 2 doses de MJ ont été administrées pendant 7 jours dans les groupes MJ uniquement, l'ADR a été administré par voie intrapéritonéale le 8ème jour après un prétraitement avec les 2 différentes doses de MJ alors que l'ADR a été administré le 8ème jour uniquement pour le groupe ADR uniquement. Le malondialdéhyde (MDA), la glutathionne (GSH), la génération de H_2O_2, la superoxyde dismutase (SOD), la catalase (CAT), la glutathionne-S-transférase (GST) aspartate, l'aminotransférase (AST), l'alanine aminotransférase (ALT), l'urée et la créatinine dans le foie, les reins et les échantillons de sérum ont été estimées selon le cas. Le tissu MDA, la génération de H_2O_2, et de l'activité TPS ont été nettement élevés tandis que la teneur en GSH, les activités de CAT et de SOD ont été considérablement réduites dans les tissus par rapport à ceux du groupe pilote ($P < 0,05$). Un prétraitement avec le MJ a amélioré les toxicités ADR, avec une réduction significative de la concentration sérique d'urée, de l'activité ALT, du niveau MDA, de la production de H_2O_2, de l'activité GST et une élévation significative du contenu GSH, des activités de la CAT et de la SOD dans les tissus d'organes. Le MJ a induit une réduction significative du niveau de la MDA et l'augmentation de la teneur en GSH dans le foie et les reins. Cette étude montre que le MJ peut jouer un effet protecteur global sur les toxicités induites par ADR dans le foie et les dans reins et que l'inhibition des dommages péroxydatifs des tissus pourrait contribuer à cet effet bénéfique.

Introduction

Jasmonates which include cis-jasmone (CJ), jasmonic acid (JA) and its esters such as methyl jasmonate (MJ) are ubiquitously occurring cyclic lipid – derived regulators in plants [1]. They are structurally related to prostaglandins in metazoans, with signal function in plant responses to abiotic and biotic stresses, as well as in plant growth and development [1].

Kim *et al* [2] reported the induction of pro-apoptotic Bcl-2 proteins in human lung cancer cells exposed to MJ treatment. Thus, it was demonstrated that MJ can counteract the radiation-induced anti-apoptotic mechanism in PC-3 cells. JAs increased

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significantly the survival of lymphoma-bearing mice and induced death in human leukemia, prostate, breast and melanoma cell lines [3], as well as in leukemic cells from chronic lymphocytic leukemia patients [3].

The mechanism of action of JAs is thought to involve the direct action on mitochondria (severe ATP depletion from mitochondrial pertubation), reactive oxygen species - mediated mechanism and the mitogen-activated protein kinase (MAPK)-dependent mechanism resulting in cell death [4]. These plant compounds are capable of inducing both necrotic and apoptotic death [3]. It has shown that JAs are capable of inducing cell death in the wild type p53-expressing cells, as well as in the mutant p53-expressing cells [4].

Adriamycin (ADR), an anthracycline antibiotic with a broad spectrum anti-neoplastic activity has been used in the treatment of variety of human neoplasms ranging from hematological malignancies and a number of solid tumours arising from breast, bile ducts, liver, oesophagus, soft tissue sarcomas and non- Hodgkin's lymphoma [5]. However, its use in chemotherapy has been largely limited due to its diverse toxicities, including cardiac, renal, hematological, hepatic, testicular and bone marrow toxicities [6]. The clinical use of ADR is limited by its dose-dependent cardiotoxicity, which leads to congestive heart failure and death [7]. Toxicity is believed to occur by ADR- induced mitochondrial dysfunctions and subsequent oxidants production [8].

Due to the above functions of MJ in plants and its demonstrated roles on neoplastic cells, we investigated the effect of methyl jasmonate in inhibiting the excessive generation of oxidative free radicals, thus providing an overall protective role in the liver and kidney toxicities induced by ADR administration in mice.

Materials and methods

Chemicals

Methyl jasmonate, adrenaline, trichloroacetic acid (TCA) were obtained from Fluka (Germany), 1-chloro-2,4-dinitrobenzene (CDNB), hydrogen peroxide (H_2O_2), reduced glutathione (GSH), thiobarbituric acid (TBA) were obtained from Sigma Chemical Co. (St Louis, MO, USA); 5'5'-dithiobis-2-nitrobenzoic acid was purchased from MRS Scientific Ltd (Wickord, U.K.). Other chemicals used were of analytical grade.

Animals and treatment schedule

Thirty adult male BALB/c mice weighing between 20 and 30g were used. They were obtained from the Drug Research Unit, Institute for Advanced Medical Research and Training (IAMRAT). The animals were maintained under normal conditions (12-hour light/dark cycle) and were fed with commercially available standard pelletted feed and water *ad libitum*.

Mice were assigned randomly distributed into six treatment groups as follows:

- Group 1: received 50mg/kg body weight of MJ for seven days.
- Group 2: received 100mg/kg body weight of MJ for seven days.
- Group 3: received 50mg/kg body weight of MJ for seven days and single dose of ADR administered on the eighth day.
- Group 4: received 100mg/kg body weight of MJ for seven days and single dose of ADR administered on the eighth day.
- Group 5: received normal saline for seven days and a single dose of Adriamycin (20mg/kg body weight) intraperitoneally on the eighth day.
- Group 6: served as control and were only administered normal saline for eight days.

Collection of blood samples and preparation of subcellular fractions from liver and kidneys

Twenty-four hours after last drug administration, all the mice were sacrificed, blood samples collected from retro orbital venous plexus and transferred into plain centrifuge tubes and allowed to coagulate by standing for one hour at room temperature. The serum was extracted by centrifugation and separated into serum tubes and stored at -20°C. The animals were dissected and liver and kidneys quickly excised, rinsed in 1.15% KCl, blotted dry on a filter paper and weighed. The tissues were then homogenized in aqueous phosphate buffer. The homogenate was centrifuged at 10,000g for 10 minutes to obtain the post mitochondrial fraction (PMF), which was later decanted into sample bottles and stored at -80°C prior to use.

Assessment of hepatic function

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined using the method described by Reitmann and Frankel [9].

Assessment of renal function

Renal function was assessed by measuring serum levels of creatinine and urea using commercial kits obtained from Randox Laboratories Ltd (Crumlin, U.K.) and based on the principles described by Henry [10] and Weatherburn [11] respectively.

Malondialdehyde, glutathione and hydrogen peroxide assays

Lipid peroxidation (LPO) and reduced glutathione (GSH) levels were determined in the PMF of the liver and kidney tissues. The MDA levels were assayed for the products of LPO by measuring thiobarbituric acid reactive substance (TBARS) formation as

described by Varshney and Kale [12]. LPO was expressed in terms of MDA equivalents usind an extinction coefficient of $1.56 \times 10^5 M^{-1}$and results were expressed as units MDA/g tissue. GSH level in tissue homogenate was assayed by measuring the rate of formation of chromophoric product in a reaction between 5',5'-dithiobis-(2-nitrobenzoate) and free sulphydryl groups (such as reduced glutathione) at 412nm as described by Jollow *et al* [13]. Hydrogen peroxide generated in tissues was determined based on Wolff's method [14]. Total protein concentration was estimated by Biuret method using Bovine Serum Albumin (BSA) as standard [15].

Assay for hepatic and renal antioxidant enzymes

Hepatic and Renal antioxidant enzyme activities were determined in the PMF. Superoxide dismutase activity was measured by the nitro blue tetrazolium reduction method of McCord and Fridovich [16]. This was based on the ability of SOD to inhibit the spontaneous oxidation of adrenaline to adrenochrome. Catalase activity was assessed according to the method of Sinha [17] and the principle was based on the ability of CAT to induce the disappearance of H_2O_2, which was followed spectrophotometrically. Glutathione S-transferase (GST) activity in the tissue homogenate was determined according to the method of Habig *et al* [18]. The method is based on the rate of conjugate formation between reduced glutathione and 1-chloro-2,4-dinitrobenzene.

Statistical analysis

Results were expressed as mean ± standard deviation (SD) of five mice per group. Data were analysed using one-way analysis of variance (ANOVA) followed by post-hoc Duncan's multiple range test for analysis of biochemical data using SPSS (12.0) statistical

Table 1: Effects of MJ on MDA level, H_2O_2 generation and GSH concentration in kidney homogenate

Treatment groups	MDA level (nmol/g protein)	H_2O_2 generation (mg/ml)	GSH concentration (μg/ml)
50MJ	3.70 ± 0.36^{a}	$13.93 \pm 0.70^{a*}$	$18.17 \pm 2.02^{a*}$
100MJ	3.36 ± 0.17^{a}	9.10 ± 0.50^{a}	$44.67 \pm 3.06^{a*}$
ADR	$6.74 \pm 0.68^{a*}$	$23.70 \pm 0.50^{a*}$	$16.83 \pm 1.44^{a*}$
50MJ + ADR	$3.11 \pm 0.26^{b**}$	21.87 ± 2.32^{b}	$36.33 \pm 16.29^{b**}$
100MJ + ADR	$4.54 \pm 0.40^{b**}$	$9.60 \pm 0.40^{b**}$	$53.67 \pm 1.15^{b**}$
UNTREATED	4.11 ± 0.48	9.60 ± 0.92	31.33 ± 4.51

*$a = p < 0.05$ when compared to the untreated group, $b = p < 0.05$ when compared with ADR. Results are expressed as mean ± standard deviation, $n = 6$. ADR = Adriamycin (20mg/kg), MJ = Methyl Jasmonate, 50MJ = MJ (50mg/kg) group, 100MJ = MJ (100mg/kg) group, 50MJ+ADR = MJ (50mg/kg) + ADR group, 100MJ + ADR = MJ (100mg/kg) + ADR group, * = significance level with untreated group, ** = significance level with ADR group.*

Table 2: Effects of MJ on MDA level, H_2O_2 generation and GSH concentration in liver homogenate

Treatment groups	MDA level (nmol/g protein)	H_2O_2 generation (mg/ml)	GSH concentration (μg/ml)
50MJ	1.49 ± 0.22^{a}	69.33 ± 6.43^{a}	59.67 ± 1.15^{a}
100MJ	$0.57 \pm 0.10^{a*}$	$82.67 \pm 2.31^{a*}$	52.83 ± 2.25^{a}
ADR	$1.70 \pm 0.42^{a*}$	$98.17 \pm 2.25^{a*}$	40.67 ± 6.1^{a}
50MJ + ADR	1.43 ± 0.35^{b}	110.00 ± 16.52^{b}	$58.17 \pm 19.19^{b**}$
100MJ + ADR	1.25 ± 0.21^{b}	106.67 ± 5.51^{b}	$92.33 \pm 2.31^{b**}$
Untreated	1.05 ± 0.05	67.33 ± 4.16	54.17 ± 4.37

*$a = p < 0.05$ when compared to the untreated group, $b = p < 0.05$ when compared with ADR. Results are expressed as mean ± standard deviation, $n = 6$. ADR = Adriamycin (20mg/kg), MJ = Methyl Jasmonate, 50MJ = MJ (50mg/kg) group, 100MJ = MJ (100mg/kg) group, 50MJ+ADR = MJ (50mg/kg) + ADR group, 100MJ + ADR = MJ (100mg/kg) + ADR group, * = significance level with untreated group, ** = significance level with ADR group.*

software. Values were considered statistically significant at $p < 0.05$.

Results

From tables 1 and 2, a significant ($p<0.05$) decrease in the renal MDA level (117% and 48%) and reduced GSH (116% and 219%) were observed in groups pretreated with 50mg/kg and 100mg/kg body weight MJ respectively compared to the ADR group. H_2O_2 generation was significantly reduced (147%) in the 100mg/kg MJ pretreatment group compared to the ADR group ($p<0.05$) but the reduction was not significant in the 50mg/kg pretreatment group. MDA level was insignificantly reduced in 50mg/kg and 100mg/kg body weight MJ treatment groups respectively when compared with untreated group ($p<0.05$). Changes in H_2O_2 generation and GSH levels were not significant between groups treated with 50mg/kg and 100mg/kg body weight when compared to the untreated groups ($p<0.05$).

There were no significant differences in the hepatic MDA level and H_2O_2 generation respectively compared to the ADR group ($p<0.05$). A significant increase was observed for hepatic GSH level ($p<0.05$) in both the 50mg/kg (43%) and 100mg/kg (127%) body weight MJ-pretreated groups compared to the ADR group. MDA level was insignificantly increased in 50mg/kg body weight MJ treatment group but significantly reduced in 100mg/kg body weight MJ treatment group when compared to the untreated group ($p<0.05$). H_2O_2 generation was insignificantly and significantly increased in 50mg/kg and 100mg/kg body weight MJ treatment groups respectively when compared to the untreated group ($p<0.05$) while reduced GSH concentration was also insignificantly increased and decreased in 50mg/kg and 100mg/kg

Table 3: Effects of MJ on the CAT, SOD and GST activities in kidney homogenate

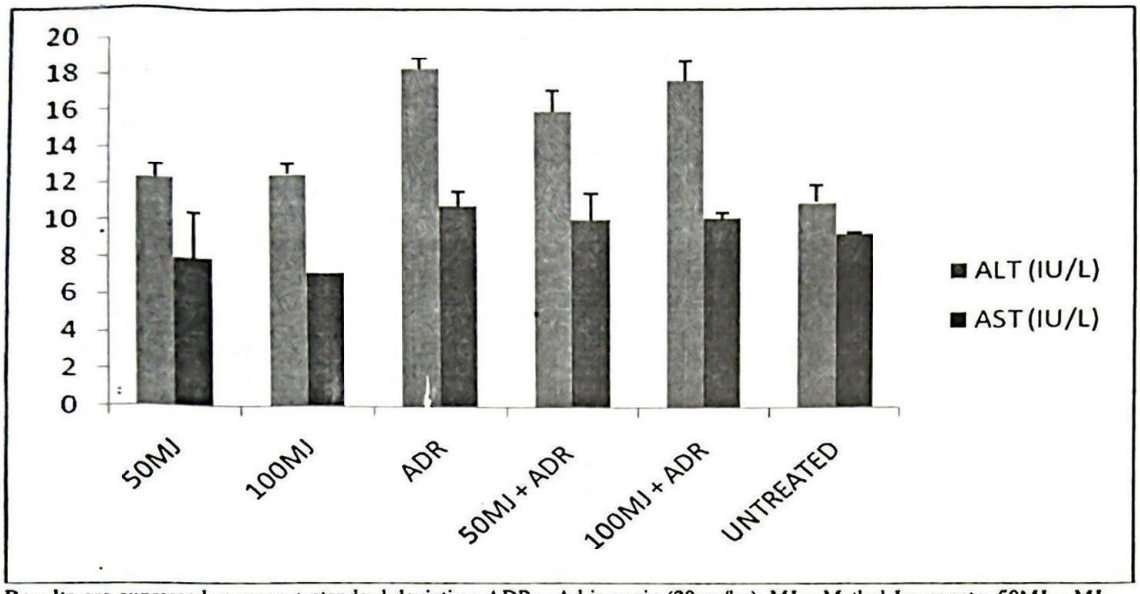
Treatment groups	CAT activity (μmol H_2O_2 consumed/min)	SOD activity (units/g tissue)	GST activity (nmole/g tissue)
50MJ	58.33 ± 8.46^{a}	$28.57 \pm 0.00^{a*}$	$0.018 \pm 0.00027^{a*}$
100MJ	50.40 ± 0.75^{a}	66.67 ± 8.25^{a}	0.028 ± 0.00086^{a}
ADR	50.27 ± 0.78^{a}	$57.14 \pm 0.00^{a*}$	$0.032 \pm 0.00119^{a*}$
50MJ + ADR	59.50 ± 18.70^{b}	71.43 ± 14.29^{b}	$0.028 \pm 0.00086^{b**}$
100MJ + ADR	65.87 ± 9.59^{b}	66.67 ± 8.25^{b}	$0.027 \pm 0.00063^{b**}$
Untreated	60.67 ± 3.11	76.19 ± 8.24	0.03 ± 0.00072

*a = $p < 0.05$ when compared to the untreated group, b = $p < 0.05$ when compared with ADR. Results are expressed as mean ± standard deviation, n = 6. ADR = Adriamycin (20mg/kg), MJ = Methyl Jasmonate, 50MJ = MJ (50mg/kg) group, 100MJ = MJ (100mg/kg) group, 50MJ+ADR = MJ (50mg/kg) + ADR group, 100MJ + ADR = MJ (100mg/kg) + ADR group, * = significance level with untreated group, ** = significance level with ADR group.*

Table 4: Effects of MJ on CAT, SOD and GST activities in liver homogenate

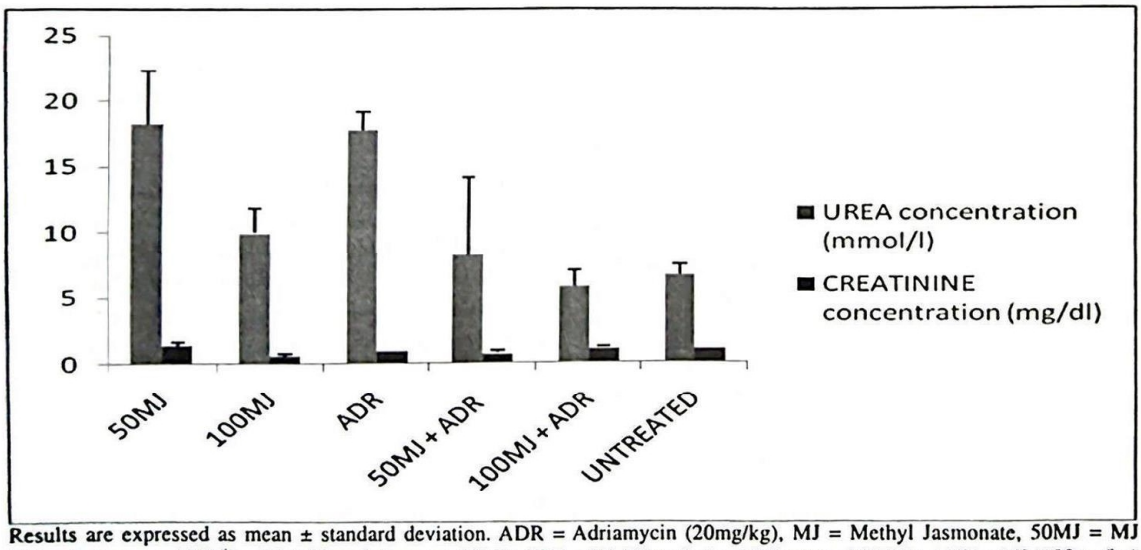
Treatment groups	CAT activity (μmol H_2O_2 consumed/min)	SOD activity (units/g tissue)	GST activity (nmole/g tissue)
50MJ	49.07 ± 3.16^{a}	$31.67 \pm 12.58^{a*}$	0.022 ± 0.00249^{a}
100MJ	47.50 ± 2.70^{a}	$46.67 \pm 23.09^{a*}$	0.032 ± 0.00188^{a}
ADR	$40.33 \pm 1.40^{a*}$	$26.67 \pm 11.55^{a*}$	0.037 ± 0.00143^{a}
50MJ + ADR	43.73 ± 6.04^{b}	46.67 ± 11.55^{b}	0.046 ± 0.01646^{b}
100MJ + ADR	45.30 ± 1.97^{b}	$53.33 \pm 11.55^{b**}$	$0.021 \pm 0.00090^{b*}$
Untreated	49.87 ± 6.61	73.33 ± 11.55	0.028 ± 0.00068

*a = $p < 0.05$ when compared to the untreated group, b = $p < 0.05$ when compared with ADR. Results are expressed as mean ± standard deviation, n = 6. ADR = Adriamycin (20mg/kg), MJ = Methyl Jasmonate, 50MJ = MJ (50mg/kg) group, 100MJ = MJ (100mg/kg) group, 50MJ+ADR = MJ (50mg/kg) + ADR group, 100MJ + ADR = MJ (100mg/kg) + ADR group, * = significance level with untreated group, ** = significance level with ADR group.*



Results are expressed as mean ± standard deviation. ADR = Adriamycin (20mg/kg), MJ = Methyl Jasmonate, 50MJ = MJ (50mg/kg)·group, 100MJ = MJ (100mg/kg) group, 50MJ+ADR = MJ (50mg/kg) + ADR group, 100MJ + ADR = MJ (100mg/kg) + ADR group

Fig. 1a: Effects of MJ on serum ALT and AST activities, and urea and creatinine concentrations



Results are expressed as mean ± standard deviation. ADR = Adriamycin (20mg/kg), MJ = Methyl Jasmonate, 50MJ = MJ (50mg/kg) group, 100MJ = MJ (100mg/kg) group, 50MJ+ADR = MJ (50mg/kg) + ADR group, 100MJ + ADR = MJ (100mg/kg) + ADR group.

Fig.1b: Effects of MJ on serum ALT and AST activities, and urea and creatinine concentrations

body weight MJ treatment groups respectively when compared to the untreated group ($p<0.05$).

In kidney, there was an insignificant increase in catalase and SOD activities in both the 50mg/kg and 100mg/kg body weight-pretreated groups

($p<0.05$) when compared to the ADR group while a significant GST activity was observed in both the 50mg/kg (14%) and 100mg/kg body (19%) weight-pretreated groups ($p<0.05$) when compared to the ADR group. Catalase activity was insignificantly decreased in 50mg/kg and 100mg/kg body weight MJ treatment groups relative to the untreated group ($p<0.05$), SOD activity was significantly and insignificantly reduced in 50mg/kg and 100mg/kg body weight MJ treatment groups respectively when compared to the untreated group ($p<0.05$) while GST activity was also significantly and insignificantly reduced in 50mg/kg and 100mg/kg body weight MJ treatment groups respectively relative to the untreated group ($p<0.05$) (Table 3).

Hepatic SOD exhibited a significant activity (100%) when compared to the ADR group ($p<0.05$) in the 100mg/kg MJ pretreated group with an insignificant increase in 50mg/kg MJ pretreated group. Hepatic catalase activity was not significantly different in both ADR pretreatment and untreated groups ($p<0.05$). Catalase activity was not significantly reduced in both 50mg/kg and 100mg/kg body weight MJ treatment groups respectively relative to the untreated group ($p<0.05$). A significant decrease in SOD activity was observed in both 50mg/kg and 100mg/kg body weight MJ treatment groups respectively relative to the untreated group ($p<0.05$) while an insignificant decrease and increase was observed in GST activity in 50mg/kg and 100mg/kg body weight MJ treatment groups respectively relative to the untreated group ($p<0.05$) (Table 4).

Serum ALT activity was significantly reduced (14%) in 50mg/kg MJ-pretreated group but the reduction was not significant in 100mg/kg MJ-pretreated group when compared to the ADR group. There was no significant difference in the serum AST activity in both the 50mg/kg and 100mg/kg MJ-pretreated groups when compared with the ADR group ($p<0.05$). Serum urea level was significantly reduced (117%) in the 50mg/kg MJ-pretreated group but not significantly reduced in the 100mg/kg body weight MJ-pretreated group compared to the ADR group ($p<0.05$). There was no significant difference in creatinine levels between the pretreated groups and ADR group ($p<0.05$). There is no difference in ALT and AST activities respectively was observed in the 50mg/kg and 100mg/kg MJ treatment groups relative to the untreated group ($p<0.05$). Urea concentration was significantly increased in 50mg/kg MJ treatment group relative to the untreated group ($p<0.05$) while a significant increase and decrease in creatinine concentration was observed in 50mg/kg and 100mg/kg MJ treatment group relative to the untreated group ($p<0.05$).

Discussion

Most anticancer agents are known to induce oxidative stress during treatment. We therefore investigate the possible chemoprotective effects and antioxidant activity of Methyl Jasmonate (MJ) on Adriamycin (ADR) – induced oxidative stress and resultant hepatic and renal toxicities.

ADR significantly increased lipid peroxidation in the liver and kidneys as observed from the significant elevation in the MDA level and H_2O_2 generation when compared to the control. This implies that when ROS is produced following ADR administration, a deleterious condition ensues where damage is caused on cellular components and membrane lipids. This leads to the formation and release of toxic reactive aldehydes (MDA and 4-hydroxynonenal [HNE]) [19]. MDA levels was depressed in the ADR groups pretreated with MJ indicating that MJ has protective potential against free radical induced lipid peroxidation in kidneys at 50mg/kg MJ while at a higher dose of 100mg/kg MJ to produced the same effect in the liver possibly by promoting cell membrane stability. Renal H_2O_2 detoxification was significant in ADR group pretreated with 100mg/kg MJ while hepatic H_2O_2 detoxification was not significant compared with the control, indicating their inability, at those doses, to counter the effects of the toxicant.

The endogenous protective proteins, SOD and CAT act in the capacity of free radical scavenging in the defense against oxidative cell injury. They are the major enzymes that catalyze the inactivation of ROS derived from redox processes of xenobiotics in the liver [20]. According to our results, the increase in CAT activity in the groups pretreated with ADR was not significant when compared with ADR group. High levels of H_2O_2 generated in the organs of intoxicated animals, was an indication of low activity of CAT and this can be due to possible substrate inhibition of the enzyme arising from elevated levels of H_2O_2 generated. The repressed activity of CAT leads to an increased SOD activity in the tissues judged from an increase in the SOD activity in a mode to limit or prevent the further generation of ROS in the tissues of ADR intoxicated animals [20].

GST, an enzyme that utilizes GSH as substrate was observed to be significantly higher in the kidneys than the liver of ADR – treated mice. This indicates that most of the available GSH in the system were used up during ROS scavenging process

imposed by oxidative stress. This was in accordance with the findings of Hou et al [19] who also reported decrease level of endogenous GSH and increase in GST activity in the kidneys of ADR intoxicated animals. MJ was able to sustain the GST activity and able to upregulate the level of GSH in the kidneys and liver tissues.

ADR induced substantial cell injury as evident in the significant increase in serum ALT activity compared to the control can be attributed to leakage of the enzyme into serum due to structural damage as the enzyme is normally located in the cytosol. Administration of MJ at different doses was able to ameliorate the damage done to the hepatocytes as evident from the decrease in the ALT activities in the MJ – treated groups [19].

Adriamycin caused significant increase in serum urea level relative to control, (17.70 ± 1.37 vs 6.60 ± 0.78, $P < 0.05$). There was a significant reduction in the urea concentration in groups administered 50mg/kg MJ and 100mg/kg MJ when compared to the ADR intoxicated animals. The effect of pretreatment with 50mg/kg and 100mg/kg MJ on serum creatinine level was not significant relative to the control. 50mg/kg and 100mg/kg MJ groups showed a significant increase and decrease in serum creatinine concentration respectively when compared to the control.

In conclusion, we report here for the first time the potential antioxidant and chemoprotective properties of Methyl Jasmonate in Adriamycin – induced toxicities.

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