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Antioxidant Profile of Rats in Mancozeb Induced Toxicity and its Amelioration by *Tridax procumbens*

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A B S T R A C T

Mancozeb, a di-thiocarbamate fungicide, is widely used in agricultural practices for the control of parasitic fungi and their spores. The present study investigates the blood antioxidant profile of rats following subacute oral mancozeb exposure and the ameliorative effect of aqueous and methanolic extracts of *Tridax procumbens* on mancozeb induced toxicity in rats. 36 wistar rats were divided into 6 groups of 6 animals, each (Control, Mancozeb (@500mg/kg) treatment group, *Tridax* aqueous extract (@300mg/kg) group, *Tridax* methanol extract (@300mg/kg) group, *Tridax* aq extract + Mancozeb group and *Tridax* met extract + mancozeb group. The rats received the fungicide and the different extracts of the plant orally for 28 consecutive days, except the control group. Subacute mancozeb exposure significantly elevated the oxidative stress marker LPO. The altered antioxidant status was evident from the depleting blood glutathione levels, significant elevation in enzymic antioxidant parameters (Catalase, GST, G6PD) and simultaneous decrease in enzymes like SOD, GPxand GR. Supplementation of *Tridax* aq. extract and *Tridax* met. extract @ 300 mg/kg per day for 28 days in mancozeb intoxicated rats had a beneficial effect on the overall antioxidant profile of the animals as witnessed by no significant alteration in LPO, blood glutathione levels and activities of various antioxidant enzymes viz. GST, GR, SOD, CAT and G6PD. Therefore, the results of the present study suggest that mancozeb administration induces pronounced oxidative stress in the rats and aqueous and methanolic extract of *Tridax procumbens* have mild to moderate ameliorative effect in the treated rats.

Introduction

Fungicides are biocidal chemical compounds or biological organisms used to kill parasitic fungi or their spores. The most important class of fungicides for controlling the fungi of agricultural crops is known to be ethylene-bis-dithiocarbamate (EBDC) forms (Sakr *et al.*, 2007). Mancozeb ([1,2-ethanediylbis] carbamodithioate]](2-)] manganese mixture with [[1,2-ethanediylbis [carbamodithioate]] (2-) zinc), belongs to the di-thiocarbamate group of fungicides. Mancozeb itself is not fungicidal but considered as a pro-fungicide, because metabolites of mancozeb, ethylene bis-isothiocyanate sulfide (EBIS) and ethylene bisisothiocyanate (EBI), are considered to be the active toxicants and interfere

with enzymes containing sulphydryl groups resulting in fatal disruption of core enzymatic processes, which inhibit or interfere with major biochemical processes within the fungal cell cytoplasm and mitochondria (Gullino *et al.,* 2010). Inspite of all the agricultural productivity and plant safety concerns, mancozeb has been found to possess many deleterious health impacts on humans as well as other non-target species exposed to residues of mancozeb. Exposure to mancozeb has been found to increase lipid peroxidation and protein carbonyl, while it reduces antioxidant enzyme activities, total antioxidant capacity, and glutathione content (Mohammadi-Sardoo *et al.,* 2018).

The usefulness of medicinal plants or plant-derived compounds has become an important alternative therapeutic approach to treat various ailments. *Tridax procumbens* of family Asteraceae commonly known as 'coat buttons' is mostly found along roadsides and waste grounds (Mundada and Shivhare, 2010). A wide range of pharmacological activities of different extracts of *Tridax procumbens* against various ailments are well documented. The extracts of the plant have also given successful results when compared with standard antioxidant compounds like ascorbic acid or gallic acid (Habila *et al.,* 2010). The methanol extract of *Tridax procumbens* exhibits higher free radical-scavenging activities which are mainly attributed to the presence of flavonoids and other polyphenols in the extracts (Jachak *et al.,* 2011). Keeping these facts under consideration, the present investigation was conducted to evaluate the effect of *Tridax procumbens* as an antioxidant, in mancozeb induced toxicity in rats.

Materials and Methods

Thirty- six adult male rats (120-150gm) were divided into six groups of six animals, each. The animals were accustomed 15days prior to the commencement of the experiment, kept in cages under standard laboratory conditions and were provided commercial rat pellets and water *ad libitum*. Group I served as control where only *ad lib* feed and water was given, Group II animals were orally drenched with mancozeb (500 mg/kg/day) dissolved in tap water, for 28 consecutive days. Group III and group IV animals were orally supplemented with aqueous and methanolic extract of *Tridax procumbens*, respectively, dissolved in water, @ 300 mg/kg/day, for the same period. In addition, Group V animals were administered mancozeb @500 mg/kg with simultaneous treatment of aqueous extract of *T procumbens* @300mg/kg and group VI animals were administered mancozeb @500mg/kg along with methanolic extract of *T procumbens* @300 mg/kg, for the same period of time. All the experimental animals were closely observed for the appearance of toxic symptoms. The nature, duration, severity of various toxic symptoms and lethality, if any were recorded during the experimental period.

Blood samples were collected on 0^{th} day of experiment from the retro-orbital sinus in heparinized vials and blood sample on 29^{th} day was collected via cardiac puncture. Erythrocyte lysate was prepared for analyzing various biochemical parameters. Haemoglobin estimation was done by the method of (Benjamin, 1985). Lipid peroxidation was estimated by determining the malonyl dialdehyde (MDA) produced using thiobarbituric acid (TBA) (Stocks and Dormandy, 1971). The glutathione peroxidase activity was measured by the method of (Hafeman *et al.,* 1974). Glutathione reductase (GR) was assayed spectrophotometrically by measuring change in absorbance at 340 nm due to NADPH utilization (Carlberg and Mannervik, 1985). Glutathione-*S*-transferase (GST) activity was analyzed by measuring the amount of conjugate formed by glutathione with CDNB (Habig *et al.*, 1974). Glucose-6-phosphate dehydrogenase was estimated on the basis of its ability to catalyze the conversion of glucose-6-phosphate and $NADP^+$ to 6-phosphogluconolactone and NADPH (Deutsch, 1978). Superoxide dismutase (SOD) activity was assayed by the ability of the enzyme to inhibit auto-oxidation of pyrogallol (Marklund and Marklund, 1974). The activity of catalase (CAT) was analyzed by the decomposition of hydrogen peroxide (Aebi,

1983). Glutathione levels were determined by the method of Beutler *et al.,* (1963).The data generated from different experiments was statistically assessed by one way analysis of variance (ANOVA) and paired t-test using SPSS 20.0 version software.

Results and Discussion

The subacute oral administration of mancozeb produced mild signs of toxicity in the rats. There was a moderate degree of anorexia followed by signs like lacrimation, listlessness, weakness of the hindlimbs and sluggish movements after 15days of mancozeb treatment.

Lipid peroxidation has been used as a measure of xenobiotic-induced oxidative stress, which may be defined as the disequilibrium between the peroxidants and antioxidants in biological system (Kelly *et al.,* 1998). Since the polyunsaturated fatty acids of the biological membrane are highly susceptible to free radical mediated oxidation, it has been postulated that redox cycling agents induce lipid peroxidation (Orth *et al.,* 1993), which in biological membranes causes impairment of membrane functioning, decreases fluidity, cause inactivation of membrane-bound receptors and enzymes and increases non-specific permeability to ions such as Ca^{2+} (Gutteridge and Halliwell, 1990).The thiobarbituric acid reactive substances (TBARS) measurement can be a good indicator of antioxidant status and oxidative stress. Malondialdehyde is an important reactive metabolite and is an indicator of lipid peroxidation. Elevated MDA level mainly occurs due to disturbance of oxidant /antioxidant balance in the biological system, which can be referred to as oxidative stress. In the present investigation, the MDA formed was significantly ($p<0.01$) higher in the mancozeb alone administered group on 29^{th} day of the study whereas, the treatment groups with aqueous and methanol extract of *Tridax procumbens* along with mancozeb had countered the increased MDA levels. Oxidative stress occurs due to the reduction of the tissue antioxidants because these agents are useful in terminating the lipid peroxidation chain reactions (Banerjee *et al.,* 2001). Induction of excess production of ROS leads to alterations in the cellular antioxidant defence system and consequently increases susceptibility to oxidative stress (Lopez *et al.,* 2007).

Superoxide dismutase is the antioxidant enzyme that catalyses the dismutation of the highly reactive superoxide anion to O_2 and to the less reactive H_2O_2 species and the peroxides are further destroyed by CAT/GPx reactions. In this study, the SOD had decreased non-significantly in mancozeb intoxicated group after 29th day of treatment as compared to the 0 day analysis**.** The co-treatment with *Tridax procumbens* methanolic extract had neutralized the altered SOD values. When a pesticide induces ROS production, the first defence is provided by SOD (against superoxide ions), and then the toxic end product of SOD which is H_2O_2, is removed by GPx (Debnath and Mandal, 2000). The GPx activity was significantly decreased ($p<0.05$) in mancozeb administered group on 29th day of treatment as compared to its control group and the respective 0^{th} day activity. However, the *Tridax procumbens* co-administered groups were unable to normalize the decreased GPx values on 29^{th} day of treatment. Decreased GPx activity in RBC lysate may have occurred due to inactivation of the enzyme protein as a result of cumulative accumulation of fungicide in the erythrocytes. The decreased enzyme level could also be attributed to the increased utilisation of this antioxidant to scavenge and neutralise the generated radical ions (Balaji *et al.,* 2014). GPx plays the major mechanism of intracellular decomposition of lipid hydroperoxides, which is crucial for preventing membrane peroxidative damage induced by lipid peroxides. The antioxidants can interfere with the oxidation process by reacting with free radicals or chelating free catalytic metals and also by acting as oxygen scavengers.

Glutathione (GSH), major intracellular non-protein thiol, acts non-enzymatically as a free radical acceptor to counter oxidative damage. GSH helps in preventing haemoglobin denaturation; it preserves the integrity of red blood cell membrane sulfhydryl

groups, and detoxifies hydrogen peroxide and oxygen radicals in and on the red blood cells (Beydemir *et al.,* 2003). Glutathione peroxidase (GPx) catalyzes the reduction and detoxification of hydrogen peroxide and lipid peroxides using GSH. With the help of GST, it forms GSH S-conjugates, which are important for protection against endogenous and exogeneous compounds (Anderson and Luo, 1998). When cellular GSH level depletes, the normal physiological endogenous formation of reactive oxygen species is largely unopposed and this may lead to cellular damage. In the present investigation, the mancozeb intoxicated group had shown significant decrease in GSH activity when compared to the control group and 0 day analysis. However, treatment with *Tridax procumbens* aqueous and methanol extract along with mancozeb had compensated for the decreased cellular GSH levels, respectively. GSH acts both as a nucleophile and a reductant, and can react with electrophilic or oxidizing species before the latter can interact with more critical cellular constituents such as nucleic acids and proteins.

The depletion of cellular level of GSH can result in cell injury as the electrophiles can then freely exert their injuring action by interacting with critical macromolecular targets through covalent binding or by initiating lipid peroxidation within the cell. Most of the cellular injury occurring after GSH depletion might actually depend on the onset of extensive oxidative processes such as lipid peroxidation (Pompella *et al.,* 2003). The altered levels were significantly reversed to normal on oral feeding of *Tridax procumbens* aqueous and methanolic extract, conferring the antilipid peroxidative activity of the extract.

Glutathione-S-transferase (GST) participates in a wide variety of bio-transformations, especially xenobiotic detoxification. It is the most versatile enzymes known for utilizing glutathione as a co-substrate. The GST activity had elevated significantly in the *Tridax procumbens* methanol extract treated group at 29th day of study compared to the 0 day value and the mancozeb exposed group had increased the GST activity non-significantly. However, the co-administered groups of mancozeb along with *Tridax procumbens* aqueous and *Tridax* methanol extract had somewhat reversed the GST levels towards normal (non-significantly). The increase in GST activity suggests the adaptive mechanism of the body to counteract oxidative stress situation. Mancozeb or other dithiocarbamate chemicals undergo detoxification through S-glucoronidation or by biodegradation to different metabolites such as carbon disulfide (CS_2), thiourea, alkylamines, ethyleneamines, and other biotransformation products (Edwards *et al.,* 1991), and the higher GST activity could be due to an enhanced potential for conjugation of mancozeb components in exposed rats.

Glucose 6-phosphate dehydrogenase (G6PD) is involved in the generation of NADPH, which is essential for the biosynthesis of reduced glutathione (GSH) from its oxidized form (GSSG). NADPH participates in cell-membrane protection and cell detoxification from xenobiotics through the gluthatione reductase-peroxidase system and helps in maintaining redox balance (Barroso *et al.,* 1999). In this study, G6PD had significantly increased in the mancozeb intoxicated rats as well as in *Tridax procumbens* aqueous extract alone treated group. The co-administered group of *Tridax procumbens* aqueous extract and mancozeb had also shown incline in G6PD activity.

The elevated G6PD activity could elevate NADPH production, thus the greater availability of NADPH might potentially increase the intensity of reduction of GSSG to GSH. The changes in the activities of primary and ancillary antioxidant enzymes suggest a positive adaptive response by mancozeb intoxicated rats to mild oxidative stress. The *Tridax procumbens* aqueous extract may have also contributed to the body's antioxidant defence system by showing an increase in G6PD activity. Thus, the combination group of *Tridax procumbens* aqueous extract along with mancozeb might have increased the G6PD activity to combat the oxidative stress situation.

Table.1 Effect of repeated oral administration of Mancozeb (500 mg/kg per day) and aqueous and methanolic extracts of *Tridax procumbens* in rats (300 mg/kg per day) respectively and their combination on lipid peroxidation, blood glutathione and Superoxide dismutase for 28 consecutive days.

Groups	LPO(nmol MDA/g Hb)		GSH(µmol/ml)		SOD(EU/g Hb)	
	0^{TH} day	29^{TH} day	0^{TH} day	29^{TH} day	0^{TH} day	29^{TH} day
GRP I	798.90±39.69^{a}	772.72±52.28^{a}	2.72±0.33^{a}	2.56±0.13^{a}	14.46±3.67^{a}	10.30±1.05^{a}
GRP II	739.32±39.76^{a}	1205.68±50.95^{c}	3.33±0.39^{a}	1.63±0.19^{b}	20.08±5.60^{a}	11.55±3.33^{a}
GRP III	786.86±32.74^{a}	935.88±31.91^{ab}	2.90±0.06^{a}	3.92±0.41^{a}	14.46±3.67^{a}	13.40±1.80^{a}
GRP IV	778.31±30.70^{a}	915.91±42.45^{ab}	2.90±0.06^{a}	2.24±0.15^{a}	20.35±3.43^{a}	14.28±2.49^{a}
GRP V	786.86±32.74^{a}	986.69±48.08^{b}	3.50±0.32^{a}	2.53±0.27^{a}	13.38±3.91^{a}	9.86±2.74^{a}
GRP VI	798.91±39.69^{a}	1047.08±29.17^{b}	3.33±0.39^{a}	2.61±0.35^{a}	14.46±3.67^{a}	14.17±2.57^{a}

GRP I –Control group, **GRP II-** Mancozeb @500mg/Kg/day, **GRP III-***Tridax procumbens* aqueous extract @300mg/Kg/day, **GRP IV-***Tridax procumbens* methanolic extract@300mg/Kg/day, **GRP V-** Mancozeb @500mg/kg/day+ *Tridax procumbens* aqueous extract@300mg/kg/day, **GRP VI-** Mancozeb @500mg/kg/day+ *Tridax procumbens* methanol extract@300mg/kg/day; The values are Mean±S.E. of six animals, unless otherwise stated.
Means with at least one common superscript (a, b, ab or c) do not differ significantly ($p<0.05$) or ($p<0.01$) between groups.

Table.2 Effect of repeated oral administration of Mancozeb (500 mg/kg per day) and aqueous and methanolic extracts of *Tridax procumbens* in rats (300 mg/kg per day) respectively and their combination on Catalase and glutathione peroxidase for 28 consecutive days.

Groups	CAT(µm of H_2O_2 decomposed/min/mg Hb)		GPx(EU/mg Hb)	
	0^{TH} day	29^{TH} day	0^{TH} day	29^{TH} day
GRP I	9071.32±340.82^{a}	9251.17±2982.62^{a}	917.19±95.44^{b}	938.72±135.61^{b}
GRP II	12063.65±958.28^{a}	64629.99±35068.91^{a}	983.92±79.06^{b}	557.54±50.39^{a}
GRP III	9165.95±320.00^{a}	106007.54±43361.58^{a}	852.08±114.24^{b}	700.11±65.75^{ab}
GRP IV	12723.24±1737.91^{a}	65863.77±23270.95^{a}	852.08±114.24^{b}	806.00±62.50^{ab}
GRP V	12063.65±958.28^{a}	79953.47±37208.94^{a}	938.84±86.12^{b}	585.33±56.77^{a}
GRP VI	11100.52±1467.84^{a}	84269.90±37173.61^{a}	852.08±114.24^{b}	610.29±47.18^{a}

GRP I –Control group, **GRP II-** Mancozeb @500mg/Kg/day, **GRP III-***Tridax procumbens* aqueous extract @300mg/Kg/day, , **GRP IV-***Tridax procumbens* methanolic extract@300mg/Kg/day, **GRP V-** Mancozeb @500mg/kg/day+ *Tridax procumbens* aqueous extract@300mg/kg/day, **GRP VI-** Mancozeb @500mg/kg/day+ *Tridax procumbens* methanol extract@300mg/kg/day; The values are mean±S.E. of six animals, unless otherwise stated.
Means with at least one common superscript (a, b or ab) do not differ significantly ($p<0.05$) between groups.

Table.3 Effect of repeated oral administration of Mancozeb (500 mg/kg per day) and aqueous and methanolic extracts of *Tridax procumbens* in rats (300 mg/kg per day) respectively and their combination on, blood glutathione a Glutathione-S-transferase, Glucose-6-phosphate dehydrogenase and Glutathione reductase for 28 consecutive days.

Groups	GST (CDNB formed/min/mg Hb)		G6PD (U/l)		GR(nmole of NADPH oxidized/min/mg Hb)	
	0^{TH} day	29^{TH} day	0^{TH} day	29^{TH} day	0^{TH} day	29^{TH} day
GRP I	126.68±6.55^{a}	147.86±17.70^{a}	1309.77±229.57^{a}	1178.65±38.56^{a}	0.012±0.001	0.011±0.002
GRP II	85.63±8.46^{a}	233.43±65.00^{a}	1068.41±110.71^{a}	1963.94±205.12^{b}	0.012±0.001	0.0089±0.001
GRP III	109.34±17.70^{a}	125.62±23.00^{a}	1141.53±60.75^{a}	1897.02±133.52^{b}	0.012±0.002	0.0173±0.004
GRP IV	81.69±8.43^{a}	173.58±31.50^{b}	1141.53±60.75^{a}	1678.36±100.79^{ab}	0.012±0.004	0.0123±0.005
GRP V	85.63±8.46^{a}	123.24±13.90^{a}	1156.24±131.91^{a}	1888.29±223.39^{b}	0.012±0.004	0.010±0.003
GRP VI	111.33±9.80^{a}	191.96±37.60^{b}	1272.27±236.56^{a}	1571.51±134.85^{ab}	0.012±0.002	0.0091±0.001

GRP I –Control group, **GRP II-** Mancozeb @500mg/Kg/day, **GRP III-***Tridax procumbens* aqueous extract @300mg/Kg/day, , **GRP IV-***Tridax procumbens* methanolic extract@300mg/Kg/day, **GRP V-** Mancozeb @500mg/kg/day+ *Tridax procumbens* aqueous extract@300mg/kg/day, **GRP VI-** Mancozeb @500mg/kg/day+ *Tridax procumbens* methanol extract@300mg/kg/day; The values are Mean±S.E. of six animals, unless otherwise stated.
Means with at least one common superscript (a, b or ab) do not differ significantly ($p<0.05$) between groups.

Glutathione reductase reduces GSSG to GSH by using nicotinamide adenine dinucleotide phosphate hydrogenase (NADPH), which is produced by G6PD. Sub-acute exposure of mancozeb had decreased the GR activity (non-significantly) but co-administration of *Tridax procumbens* aqueous extract along mancozeb had countered the changes incurred in GR activity towards normal. The *Tridax procumbens* aqueous extract producing more NADPH by increasing the activity of G6PD could also have further contributed to the conversion of GSSG to GSH by Glutathione reductase enzyme, although the enhanced GR activity was unable to restore the blood GSH levels.

The analysis of redox markers in the present inquisition revealed significant oxidative stress, reflected by an increase in hydroperoxides (lipid peroxidation marker) and a significant decrease in GSH levels. It could be suggested that antioxidant enzyme activities are modulated by the presence and the magnitude of oxidative stress following pesticide exposure. A significant inverse relationship exists between the extent of lipid peroxidation and glutathione status. The blood glutathione levels in the present study showed decline on mancozeb exposure but the situation was reversed with treatment of aqueous and methanolic extract of *Tridax procumbens.* The corresponding decline in the activity of antioxidant enzyme viz. superoxide dismutase, was to a certain level reversed by *Tridax procumbens* methanol extract. GPx that catalyzes the hydrogen peroxide, produced by superoxide dismutase had also shown a significant decline, which could be due to over-utilization of these antioxidant enzymes, but this over utilization that led to the decrease in their concentration was still not sufficient to overcome the oxidative stress caused mancozeb. Decreased activities of these enzymes indicate the failure of the primary antioxidant system to act against free radicals. Auxillary enzymes contribute through glutathione synthesis or the glutathione redox cycle to regenerate glutathione from its oxidized form. Mancozeb administration resulted in significant elevation in the activities of these enzymes viz. glutathione-*S*-transferase and glucose-6-phosphate dehydrogenase. The cell has several mechanisms to alleviate the effects of oxidative stress, either by repairing the damage or by directly diminishing the occurrence of oxidative damage by means of enzymatic and non-enzymatic antioxidants. Mancozeb led to substantial activation of defence systems against ROS which demonstrates a general increment of antioxidant potential under mancozeb exposure. However, antioxidant defences seem to be insufficient to provide full protection against oxidation. The data clearly demonstrates induction of mild oxidative stress in rat erythrocytes under exposure to mancozeb as evidenced by enhanced levels of ROS-oxidized proteins and lipids and stimulated decreases in the activities of the principal antioxidant enzymes blood glutathione, SOD, and GPx and increased in the activity of GST and G6PD. However, both the aqueous and methanolic extract of *Tridax procumbens,* to a certain extent, provided protection against the oxidative insult produced by mancozeb, either by supporting the body's antioxidant defence system by increasing the activity of auxillary antioxidant enzymes or by itself acting as a free radical scavenger.

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