Harungana Madagascariensis Stem Bark Confers Ameliorative Potential against Subchronic Dichlorvos Induced Oxidative Stress

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ABSTRACT

Dichlorvos (DDVP) is an organophosphate insecticide known to cause oxidative stress, which can have a number of negative public health consequences. *Harungana madagascariensis* (HM), also known as dragon blood tree/amuje, is a plant with antioxidant and anti-inflammatory properties found to reduce oxidative stress in a variety of scenarios. In this study, we looked at the ability of HM stem bark extract to reduce subchronic DDVP induced oxidative stress in rats. Forty (40) Wistar albino rats were randomly assigned into polyphenylene cages Eight (8) per cage in five groups namely; control (group 1), group 2 (DDVP exposed), and treatment groups (groups 3, 4, 5 'DDVP exposed' + 50 mg/kg, 100 mg/kg, 150 mg/kg extract, respectively). Male rats were treated with DDVP (10 mg/kg b.w) except for the control. Both the stressor/toxicant and extract were administered orally throughout the study duration of 28 days. At the end of the study, rats were sedated with chloroform, and blood and organ samples were collected for biochemical analysis. Biomarkers of oxidative stress, such as SOD, CAT, GPx, MDA, and NO, were meticulously evaluated in liver, kidney, and serum. Hormonal indicators, such as FSH, LH, and TES, were assessed in serum too. The result revealed that HM stem bark extract has antioxidant and anti-inflammatory properties that can protect against subchronic DDVP-induced oxidative stress. The extract also influences increased SOD, CAT, and GPx activity and decreased MDA and NO levels in DDVP exposed rats' liver, kidney, and serum. Additionally, it decreased FSH, LH, and TES levels in DDVP-exposed rats suggesting a potential hormonal protective property. The results are indicative that HM stem bark extract has potential as a therapeutic agent for treatment of subchronic DDVP-induced oxidative stress and its related adverse health conditions. Advance studies are required to elucidate the mechanisms of action of HM stem bark extract and to determine its efficacy in human populations.

Keywords: Ameliorative, *Harungana madagascariensis*, Dichlorvos, Oxidative stress, Therapeutic

INTRODUCTION

Oxidative stress has been described as an imbalance between antioxidant defenses and reactive oxygen species, which is indicative of the negative consequences of many pesticides in the environment [1]. A

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prominent organophosphorus pesticide known as dichlorvos (DDVP) is one of these pesticides, which is synonymous to agrochemicals including bactericides, fungicides, herbicides, insecticides, and rodenticides [2]. Every year, these pesticides amounting to approximately 2 million tons are used across the world accounting for China, United State of America and Argentina as the top three nations that produce pesticides following the growing global need for pesticides as well as the ever-increasing global population [3].

Accordingly, pesticides significant impact on many ecosystems, species, and human health has received little attention despite their widespread usage in agriculture and non-agricultural settings across the globe [4]. Given the significant danger of direct exposure for people who work with pesticides and its link to cellular malfunction or damage due to its ability to induce oxidative stress with the liver being the most susceptible to the harmful effects in subchronic dichlorvos exposure, its crucial to diverge into possible ways through which this effect may be cushioned or ameliorated.

The claim that *Harungana madagascariensis* (HM) have the potential to reduce the negative effects of toxic chemicals is supported by many researchers [5] and as such, elucidating the potential of HM stem bark as a therapeutic agent against subchronic DDVP induced oxidative stress is thus the objective of this research as we hope to shed light on the protective mechanisms performed by the bioactive chemicals in this stem bark by examining important markers of oxidative stress. Therefore, a vital step toward sustainable and holistic approaches to environmental and human health is the research of natural medicines, such as HM stem bark, in light of the growing global concerns about pesticide exposure [6,7].

In African tradition, several plants are in use for treatment of many ill health conditions owing to their recognized medicinal properties as these plants can take forms of decoctions, powders or ointments [8]. *Harungana madagascariensis* is from the family known as Hypericaceae, and goes by a general name as the dragon's blood tree, orange-milk tree, and haronga [9]. It is a small-medium tropical shrub having a fine stellate hairs and ovate lateral leaves. Africa among other developing nations still rely on medicinal plants such as HM as a first line of defense against a wide range of illnesses, inclusive of the deadliest diseases like malaria and typhoid, especially in some African countries such as Cameroon, Nigeria, Ghana, or Madagascar [10,11]. Folks in these countries widely make use of HM for a variety of medicinal purposes as it displays a wide variety of pharmacological actions, due to its main pigmentation known as harunganin extracted from the stem bark of the HM plant marking the beginning of chemical studies of this plant [12]. Although these medicinal plants have been studied extensively from time immemorial, however no exhaustive study of the stem bark of HM plant has been conducted in light of its potential utility on ameliorative potential against subchronic dichlorvos induced oxidative stress. Therefore, this study seeks to ascertain effects of HM stem back extract in the liver, kidney and serum of rats exposed to dichlorvos through the activities of some oxidative stress biomarkers such as SOD, GPx, CAT, NO etc.

The *H. madagascariensis* is popularly known as Uturu among the Igbo tribe of the southeastern Nigeria where it is usually presented as cold or hot infusion for the treatment of illnesses such as dysentery, typhoid fever, diarrhea, gastrointestinal issues etc. The decision to study its ameliorative potential of HM stem bark extract against subchronic dichlorvos induced oxidative stress is to verify the 7 credibility of local herbalists' statements regarding the efficacy of similar preparations based on folklore by examining solely the methanolic extracts using the customary method of extraction [13].

Dichlorvos, with its chemical nomenclature as 2,2-dichlorovinyl dimethyl phosphate (DDVP), is globally applied in agricultural and residential settings for pesticides control, and as argued, has shown to be an effective inhibitor of the enzyme acetylcholinesterase (AchE) [14], which is essential for proper nerve signaling, as nervous system difficulties, respiratory issues. Also, reproductive toxicity maybe just one of the acute and chronic health impacts associated with dichlorvos exposure.

Accordingly, there are multiple pathways via which subchronic dichlorvos exposure might cause oxidative

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stress; AchE inhibition is one possible mechanism as acetylcholine is generally degraded by AchE, a neurotransmitter involved in muscle contraction and neuronal transmission. Therefore, inhibiting AchE causes acetylcholine to build up, which in turn can enhance free radical generation [15]. As such, this research investigated the ameliorative possibility of HM stem bark extract on subchronic DDVP-induced oxidative stress in rats. Hence, we hypothesized that the plant extract would stimulate antioxidant enzymes activities while reduces the levels of oxidative stress biomarkers evidenced in protection against DDVP-induced hormonal disruption. The study equally explored the experimental methodology, provided data from the experiments and analyze the ramifications of its findings in details.

METHODOLOGY

Study Design

This study employed a randomized controlled design to ensure that any observed effects could be attributed to the specific intervention rather than chance [16], while the experimental design involved five groups including a normal or control group (group 1), a DDVP exposed or negative control group at 10 mg/kg (group 2), and three treatment groups exposed to DDVP at 10 mg/kg along with different doses of HM extract (groups 3-5). The study duration was 28 days, carefully planned to capture the sub-chronic effects of DDVP and the potential ameliorative actions of HM.

Animals and experimental design

Male Wistar Albino rats were purchased from the central animal house, University of Port Harcourt, Nigeria. They were housed in propylene cage with controlled environmental conditions of 37^0 C and 12 hours light and dark cycle and equally allowed water and feed ad libitum after acclimatization of the rats for 14 days prior to the study. The rats were provided rat chow (vital Grower Mash) feed produced by Grand Cereal Limited, Jos, Plateau State, Nigeria. The insecticide for the study with brand name DD-Force containing DDVP as its active ingredient was purchased from the agrochemical shop at Choba market, Port-Harcourt, River State, Nigeria. 2,2- dichlorovinyl dimethyl phosphate (DDVP) administration was done through oral gavage to mimic real-world exposure which includes inhalational procedure [17]. HM extract was prepared and administered in accordance with established protocols, considering the specified dosage for each treatment group. The grouping and treatment protocol was;

Group 1: Control group (no DDVP exposure and no *H. madagascariensis* extract)

Group 2: DDVP (10 mg/kg b.w) exposure only

Group 3: DDVP exposure + 50 mg/kg b.w *H. madagascariensis* extract

Group 4: DDVP exposure + 100 mg/kg b.w *H. madagascariensis* extract

Group 5: DDVP exposure + 150 mg/kg b.w *H. madagascariensis* extract

Preparation of *H. Madagascariensis* Stem Bark Extract

H. madagascariensis stem bark was gathered from mature *Harungana madagascariensis* trees in pharmacology botanical garden, University of Port-Harcourt, Nigeria. It was dried under shade, ground into fine powder after which it was extracted with 70% methanol using a soxhlet extractor. The extract was concentrated under reduced pressure and stored at -20° C for the study.

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Data Validity and Reliability

To enhance data validity and reliability, rigorous control measures were implemented, including standardized animal housing conditions, consistent administration protocols, and careful calibration of equipment used for measurements.

Statistical Analysis

Data from the study were expressed as mean ± standard error of the mean (SEM). Statistical analysis included one-way ANOVA and for multiple comparisons, Tukey's post hoc test was adopted and p-value < 0.05 was considered statistically significant.

Ethical Considerations

The work complied with ethical guidelines for using animals in research. All animal care and procedures were carried out in compliance with the National Research Council's Guide for the Care and Use of Laboratory Animals, which was approved by the Institutional Animal Care and Use Committee at the University of Port-Harcourt in Nigeria.

RESULTS OF THE STUDY

Effect of *H. Madagascariensis* Extract in Oxidative Stress Biomarkers of Liver Enzymes

Table 1.1: Effect of *H. madagascariensis* extract in oxidative stress biomarkers on liver enzyme

GROUPS	SOD (U/ml)	CAT (U/ml)	GSH (nmol/l)	GPx (nmol/l)	MDA (nmol/l)	NO (nmol/l)
GROUP 1	0.44±0.01^{c}	5.43±0.05^{d}	1.22±0.09^{c}	0.055±0.004^{bc}	0.31±0.01^{a}	5.41±0.03^{a}
GROUP 2	0.20±0.02^{a}	2.88±0.06^{a}	0.56±0.06^{a}	0.025±0.002^{a}	0.61±0.00^{c}	10.98±0.09^{c}
GROUP 3	0.33±0.01^{b}	3.26±0.07^{b}	0.77±0.01^{b}	0.035±0.005^{a}	0.58±0.01^{c}	9.05±0.22^{b}
GROUP 4	0.33±0.01^{b}	3.33±0.09^{b}	1.04±0.03^{c}	0.047±0.002^{b}	0.48±0.01^{b}	8.90±0.12^{b}
GROUP 5	0.43±0.01^{c}	4.79±0.12^{c}	1.22±0.05^{c}	0.063±0.004^{c}	0.33±0.01^{a}	5.41±0.06^{a}

Data were expressed as mean±SE (Standard Error) of n=5 determination. ^{abcde} *represent groups with different superscript and values in the same column having the same superscript letter were not significantly different at p<0.05. Group 1: Normal or control (healthy rats), Group 2: DDVP exposure rats at 10 mgkg-1b.w through ingestion by oral gavage with no intervention (negative control), Group 3: DDVP exposure + 50 mgkg-1 H.madagascariensis extract (treatment group), 4: DDVP exposure + 100 mgkg-1 H.madagascariensis extract (treatment group), 5: DDVP exposure + 150 mgkg-1 H.madagascariensis extract*

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(treatment group).

The environment including water, soil, air as well as humans bears the negative burden of uncontrolled pesticide use which pose adverse health challenge to even non-target organisms [18, 19]. As compared to the control group in table 1.1 above, the DDVP-exposed group exhibited a substantial decrease in the activities of glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD). The DDVP-exposed group may have been under oxidative stress based on the lower activity of these enzymes, which are involved in the detoxification of reactive oxygen species (ROS). Also, the levels of SOD in the above table were considerably higher in groups (3, 4, and 5) treated with HM extract than in the negative control (group 2). This is an indication of improvement in the antioxidant defense mechanism against oxidative stress.

Furthermore, table 1.1 showed that in the treatment groups, administration of HM extracts remarkedly boosted the activities of SOD, CAT, and GPx. This showed that the extract from HM may have antioxidant properties that shielded the rats' organs from oxidative damage. Exposure to DDVP resulted in considerably higher amounts of a lipid peroxidation marker known as malondialdehyde (MDA), compared to control. This indicated that DDVP-exposed group was undergoing lipid degradation. The group exposed to DDVP experienced a significant reduction in MDA levels following the administration of HM extract. This also implied that the extract of HM may assist in shielding the liver from lipid related harm and hence can protect the liver from lipid damage. When comparing the DDVP-exposed group to the control group, there was a substantial rise in the levels of nitric oxide (NO), a hallmark of inflammation. This indicated that there was inflammation in the group exposed to DDVP. The group exposed to DDVP experienced a significant reduction in NO levels following the administration of HM extract. This implied that the extract from HM has anti-inflammatory qualities.

Effect of *H. Madagascariensis* Extract in Oxidative Stress Biomarkers on Kidney Enzyme

Table 1.: Effect of *H. madagascariensis* extract in oxidative stress biomarkers on kidney enzyme

GROUPS	SOD (U/ml)	CAT (U/ml)	GSH (nmol/l)	GPx (nmol/l)	MDA (nmol/l)	NO (nmol/l)
GROUP 1	0.47 ± 0.01^{c}	1.91 ± 0.01^{d}	1.24 ± 0.01^{c}	0.056 ± 0.000^{c}	0.37 ± 0.01^{a}	4.85 ± 0.11^{a}
GROUP 2	0.19 ± 0.00^{a}	0.72 ± 0.01^{a}	0.59 ± 0.02^{a}	0.025 ± 0.003^{a}	0.64 ± 0.00^{d}	10.20 ± 0.04^{d}
GROUP 3	0.24 ± 0.01^{a}	1.01 ± 0.01^{a}	0.97 ± 0.03^{b}	0.040 ± 0.004^{b}	0.58 ± 0.01^{c}	9.45 ± 0.25^{c}
GROUP 4	0.37 ± 0.01^{b}	1.78 ± 0.02^{b}	1.24 ± 0.01^{c}	0.056 ± 0.002^{c}	0.52 ± 0.02^{b}	7.70 ± 0.09^{b}
GROUP 5	0.41 ± 0.04^{bc}	1.23 ± 0.02^{c}	1.57 ± 0.01^{d}	0.071 ± 0.001^{d}	0.52 ± 0.01^{b}	4.86 ± 0.03^{a}

Data were expressed as mean±SE (Standard Error) of n=5 determination. ^{abcde} *represent groups with different superscript and values in the same column having the same superscript letter were not significantly different at p<0.05. Group 1: Normal or control (healthy rats), Group 2: DDVP exposure rats at 10 mgkg-1b.w through ingestion by oral gavage with no intervention.*

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(negative control), Group 3: DDVP exposure + 50 mgkg-1 H.madagascariensis extract (treatment group), 4: DDVP exposure + 100 mgkg-1 H.madagascariensis extract (treatment group), 5: DDVP exposure + 150 mgkg-1 H.madagascariensis extract (treatment group).

The findings in table 1.2 above demonstrated that, in comparison to the control group, the DDVP exposure group had considerably lower SOD, CAT, and GPx activity. Since these enzymes aid in the detoxification of reactive oxygen species (ROS), it is possible that the kidneys of the DDVP exposure group were under oxidative stress due to their lower activity of these enzymes. Also, the treatment groups showed that administration of HM extract remarkably boosted the activity of SOD, CAT, and GPx. This showed that the extract from HM have antioxidant qualities and may be able to shield the kidneys from oxidative damage.

When comparing the DDVP exposed group to the control group, there was a substantial increase in MDA levels, a marker of lipid peroxidation. This may indicate that the kidneys of the group 2 rats were being damaged by lipids. However, the administration of HM extract significantly reduced the levels of MDA in the treatment groups. This showed that the extract from HM may be able to shield the kidneys against lipid damage. In addition, our findings in DDVP exposed rats in group 2 showed that the NO levels—an indication of inflammation, were noticeably higher than those of the control group. This implied that renal inflammation was present in the DDVP exposure group. However, administration of HM extract dramatically reduced NO levels in DDVP exposure groups. This indicated that the extract from HM have anti-inflammatory qualities.

Effect of *H. Madagascariensis* on Serum Hormonal Biomarkers

Table 1.3: Effect of *H. madagascariensis* on serum hormonal biomarkers

GROUPS	FSH (mIU/ml)	LH (ng/ml)	TES (ng/ml)
GROUP 1	0.31 ± 0.10^{a}	0.88 ± 0.07^{a}	1.13 ± 0.18^{ab}
GROUP 2	0.60 ± 0.11^{b}	1.60 ± 0.28^{c}	2.01 ± 0.59^{c}
GROUP 3	0.46 ± 0.08^{ab}	1.28 ± 0.22^{b}	1.74 ± 0.01^{b}
GROUO 4	0.42 ± 0.13^{b}	0.94 ± 0.08^{a}	1.21 ± 0.18^{a}
GROUP 5	0.35 ± 0.05^{a}	0.92 ± 0.10^{a}	0.81 ± 0.15^{a}

Data were expressed as mean±SE (Standard Error) of n=5 determination. ^{abcde} represent groups with different superscript and values in the same column having the same superscript letter were not significantly different at p<0.05. Group 1: Normal or control (healthy rats), Group 2: DDVP exposure rats at 10 mgkg-1b.w through ingestion by oral gavage with no intervention (negative control), Group 3: DDVP exposure + 50 mgkg-1 H.madagascariensis extract (treatment group), 4: DDVP exposure + 100 mgkg-1 H.madagascariensis extract (treatment group), 5: DDVP exposure + 150 mgkg-1 H.madagascariensis extract

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(treatment group).

According to the findings in table 1.3 above, the DDVP exposed group's levels of testosterone (TES), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were significantly higher than those of the control group and this suggests that the DDVP exposure group was experiencing hormonal imbalance. In the DDVP exposure group, the administration of HM extract dramatically reduced the levels of FSH, LH, and TES. This showed that the extract from HM may be able to shield the reproductive system against hormonal disturbances. According to our findings, from the table above, HM extract may have anti-inflammatory, hormonally protective, and antioxidant qualities. These characteristics might help with the management of oxidative stress brought on by subchronic dichlorvos exposure.

Effect of *H. Madagascariensis* Extract on Liver Smear for the Histopathology Examination

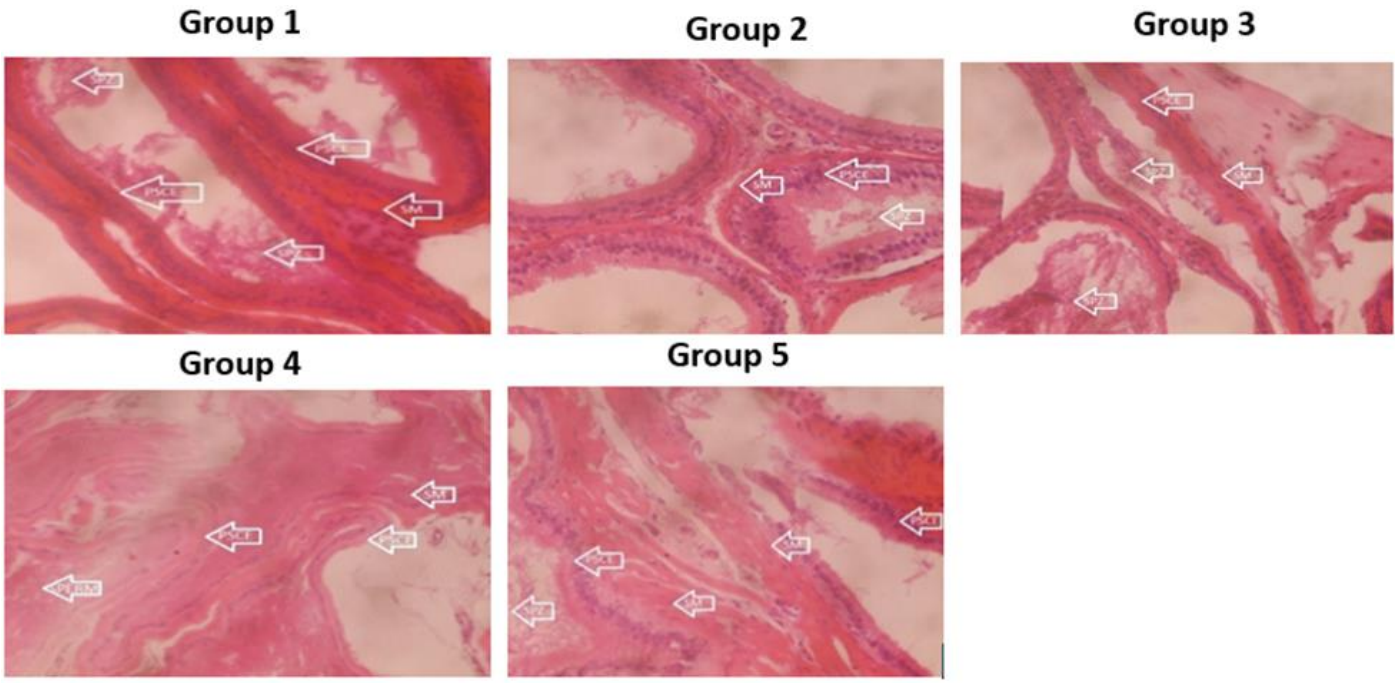

Plate 1.1: Photomicrograph of liver smear for the histopathology examination of male Wistar albino rat. Group 1: Normal or control (healthy rats), Group 2: DDVP exposure rats at 10mgkg^{-1}b.w through ingestion by oral gavage with no intervention (negative control), Group 3: DDVP exposure + 50mgkg^{-1} H.madagascariensis extract (therapeutic group), 4: DDVP exposure + 100mgkg^{-1} H.madagascariensis extract (therapeutic group), 5: DDVP exposure + 150mgkg^{-1} H.madagascariensis extract (therapeutic group).

The above photomicrograph on plate 1.1 taken at 4 x100 magnification on the smeared testicular cell for histology examination of male Wistar albino rat, showed lined epididymis tubules with pseudostratified columnar epithelium, smooth muscles and spermatozoa. Succinctly, the groups exposed to DDVP presented a notable histological lesion as a result of the toxic damage caused by the stressor (dichlorvos) when compared to the control with normal tissue architecture. However, the treatment groups (3,4,5) showed moderate tissue lesion when compared to the control, this may be attributed to the effect of the administered extract with evidence of restoring the spermatozoa. This further confirms to the fact that that HM is a

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potential agent that can be used to stabilize the reproductive hormonal dysfunction.

DISCUSSION

The results of the study show that the HM extract proffers protective effect against oxidative stress induced by DDVP exposure on rats. This result aligned with a study that reported the protective effect of cinnamaldehyde on inflammatory response, oxidative stress and apoptosis in mice liver [20]. In the liver and kidney, the extract was able to dramatically lower the levels of MDA and NO while also dramatically increasing the activities of SOD, CAT, and GPx. These results point to the possibility of using HM extract as a medicinal agent to alleviate oxidative damage brought on by DDVP. Also, this study collaborated with the result on reporting gene upregulation and protein expression in human fibroblasts and skin explants through administration of HM with retinol-like properties [21]. The study also found that HM extract had a significant effect on serum hormonal biomarkers. The serum levels of TES, LH, and FSH were all considerably reduced by the extract. These results imply that HM extract might be used therapeutically to treat hormonal imbalances.

All things considered, the study's findings also point to HM extract as a potentially useful natural supplement for the management of hormonal abnormalities and oxidative stress damages or disorder. This is consistent with the finding that confirmed HM extract demonstrated hypotensive and antioxidant properties in response to sodium fluoride-induced hypertension rats [22], suggesting that the plant may be useful in treating hypertension related to oxidative stress. The result of this study also aligns with the findings that chlorpyrifos, cypermethrin, and imidacloprid being a known pesticide just like dichlorvos is implicated in Mitochondrial dysfunction and oxidative stress in liver of male albino rats following subchronic exposure [23]. In another study, it was reported that the antioxidant capacity of HM is quite high as there was an improvement in the antioxidant activity and overall quality of the stem bark crude extract compared to the gold standard, ascorbic acid [24]. In addition to being superior antioxidant medications to the gold standard gallic acid, HM demonstrated robust DPPH, as the author affirmed that the plant is packed with antioxidants, which help to manage oxidative stress. Another study also affirmed that extracts of HM can prevent and manage acetaminophen toxicity in the kidneys and liver, and that if the plant extract is combined with the antioxidant's selenium and ascorbic acid, it may be able to protect and treat the organs at lower doses of 100 mg/kg and 200 mg/kg, respectively, in the event of liver or kidney damage caused by acetaminophen [25]. The above also aligned with the findings of study which demonstrated the potential of *Cissampelos capensis* and *Pleiocarpa pycantha*. However, this study differs from the conventional approach whereby more than one plant extract like the study of *Cissampelos capensis* and *Pleiocarpa pycantha* extracts employed in a study as a potential hepatoprotective agent in treatment of an oxidative damage caused by nitrosamines [26].

Other researchers also confirmed that an aqueous extract of HM pre-treated rats showed a significant protective effect against isoproterenol-induced myocardial infarction [27,28,29]. As such, these findings may be linked to an increase in antioxidant defense of HM and how it reverses the pathophysiology of myocardial infarction. In relation to other studies, this study stands out amongst its contemporaries given that while other studies in this field have long relied on DDVP exposure as a model of oxidative stress, this study was able to address the problem of dichlorvos exposure while identifying the ideal dosage by testing a range of HM extract concentrations. This is significant because, while some herbal extracts may be beneficial, others may be toxic if used in excess.

In the same vein, the effects of HM extract were thoroughly evaluated in the study, which examined multiple oxidative stress indicators; more information is gleaned from this than from studies that evaluate a small number of biomarkers. As such, the contribution to knowledge is significant as this study was able to showcase more about the possible medicinal benefits of HM extract since it evaluated blood hormone

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indicators. This is significant because oxidative stress can be exacerbated by hormone abnormalities. Finally, because the study was carefully planned and closely monitored allowing for more confidence in the outcomes, the results can be relied upon. The findings of this study strongly imply that HM extract can shield the liver and kidneys from DDVP-induced oxidative damage. Additional data suggests that the extract may have a therapeutic impact on hormonal issues. More studies are required to elucidate the mechanisms of action of HM stem bark extract in mitigating the oxidative damage caused by dichlorvos toxicity and to determine its efficacy in human populations.

CONFLICT OF INTEREST

There are no conflicts of interest in this study.

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