

Morinda Citrifolia (Noni) attenuated transcriptional and degenerative markers of cardiac toxicity in bisphenol A treated male wistar rats

Adeyemi Oluwafemi Oyabambi^{*}, Blessing Boluwatife Aindero, Boluwatife Eunice Fashetan, Kofoworola Tinuola Oni

Department of Physiology, College of Health Sciences, University of Ilorin, Ilorin, Nigeria

ARTICLE INFO

Keywords:

Degenerative markers
Transcriptional factor
Epigenesis
Morinda citrifolia
Bisphenol A
Wistar rats

ABSTRACT

Bisphenol A (BPA) is an endocrine disruptor that causes metabolic disruption. It is widely used in the manufacturing industry as an internal protective lining for food and beverage cans. *Morinda citrifolia* (Noni) is a known ethno-medicinal plant of Pantropical origin. The aim of this study was to investigate the effect of Noni aqueous extract (NAE) on transcriptional and degenerative markers of cardiac toxicity in Bisphenol A treated male Wistar rats. Twenty-four male Wistar rats were randomly assigned into four groups as: Control (Ctr: normal chow + vehicle: Olive oil), BPA (7 g/kg, orally), (NAE:500 mg/kg; orally), and NAE: (500 mg/kg + BPA;7g/kg orally). After six weeks of administration, animals were anesthetized with 0.8 mg Phenobarbitone intraperitoneally and blood was collected by cardiac puncture. Plasma and cardiac homogenate were sampled and data were analyzed using a one-way ANOVA followed by Bonferroni's Post hoc test. Results are expressed as mean $\pm$ standard error of mean (SEM) and $p < 0.05$ were accepted as significant. Bisphenol A reduced significantly plasma and cardiac histone deacetylase (HDAC), Nitric oxide (NO) and adenosine and increased triglycerides (TG), lipoprotein (a) or Lp(a), tumor necrotic factor alpha (TNF- α), uric acid (UA), and (malondialdehyde) MDA when compared with control and noni-treated group. NAE increased HDAC and NO significantly compared to the control while reducing significantly TNF- α , catalase, MDA, TG, and Lp(a). In conclusion, NAE reduced Bisphenol A worsening cardiovascular risks through a significant positive epigenetic HDAC expression and increased neovascularization activities.

1. Introduction

Cardiovascular diseases are the leading cause of morbidity worldwide (Vaduganathan et al., 2022). Cardiotoxicity is the term used to describe cardiac muscle damage, which affects the effectiveness of the heart and makes the heart less efficient in pumping blood, a major risk factor for cardiovascular diseases (Erbaş et al., 2022). Metabolic syndrome which includes abdominal obesity, dyslipidemia, hypertension, and poor glucose tolerance are risk factors for cardiovascular diseases (Ilkun and Boudina, 2013). The influence of environmental contaminants on humans has been proposed as a cause of cardiovascular diseases (Bhatnagar, 2017). Millions of tons of plastic are manufactured each year, which exposes people to hazardous compounds on a daily basis (Leslie et al., 2022). Toxins act as a mediator for cardiotoxicity and

reduces the number of active myocytes, which reduces pumping efficiency in the cardiovascular system. These toxins also cause oxidative damage and lipid peroxidation, leading to swelling of the cells. The primary pathophysiological mechanisms of cardiotoxicity include the production of oxygen free radicals, calcium excess in myocytes and lack of antioxidant systems like catalase, superoxide dismutase (Erbaş et al., 2022). Bisphenol A is a synthetic phenolic organic compound which acts as an endocrine disrupting chemical (EDC). It is one of the most widely used chemicals in consumer products. It is added to or employed as monomers in the manufacture of epoxy resins and polycarbonate polymers (Okugbe and Songhe 2019). Humans are well known to be exposed to BPA through food (the main source), drinks, infant bottles, food can linings, and industrial uses such water pipes (von Goetz et al., 2010; Gao and Wang, 2014).

Abbreviations: HDAC, histone deacetylase; NO, nitric oxide; TG, triglycerides; Lp(a), lipoprotein (a); TNF- α , tumor necrotic factor alpha; UA, uric acid; MDA, malondialdehyde; BPA, bisphenol A; NAE, noni aqueous extract; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; EDC, endocrine disruptor chemical; CVD, cardiovascular disease.

^{*} Corresponding author.

E-mail address: oyabambi.ao@unilorin.edu.ng (A. Oluwafemi Oyabambi).

<https://doi.org/10.1016/j.jff.2023.105865>

Received 4 August 2023; Received in revised form 14 October 2023; Accepted 17 October 2023

1756-4646/© 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Bisphenol A's ability to penetrate food or the environment is increased by the hydrolysis of its ester linkages in high-temperature, acidic, and basic environments (Fenichel et al., 2013; von Goetz et al., 2010). The study of BPA's toxicity is expanding quickly and one new area of focus is how it affects the cardiovascular system. In mice, chronic exposure to BPA has been linked to blood pressure changes, atherosclerosis, and cardiac remodeling. The underlying mechanisms may change how the heart handles Ca^{2+} , ion channel inhibition or activation, oxidative stress, and alterations to the genome and transcriptome (Gao and Wang, 2014). By accelerating the establishment and spread of risk factors and CVDs, BPA exposure endangers human health. These EDC binds to estrogenic receptors such as $\text{ER}\alpha$, $\text{ER}\beta$, $\text{ER}\gamma$ G-protein-coupled estrogen receptor 30, and peroxisome proliferator-activated receptor gamma (Fonseca et al., 2022). Although the precise mechanisms of action are still unknown, BPA has been found to produce adipogenesis, inflammation, oxidative stress, pancreatic cell malfunction, and insulin resistance. BPA exposure has become a major public health problem, and it's even believed that BPA's disruptive effects may be dangerous to the cardiovascular system (Fonseca et al., 2022).

Morinda Citrifolia (Noni fruit) also known as Indian mulberry is commonly grown in the tropical countries. It is a small to medium sized common plant which is oval in shape, soft, translucent-greyish with about 90 % water content. Noni fruit is 4–10 cm in length, 3–8 cm in circumference with many small drupes fused to its rough surface (Choo et al., 2023). From ancient times, Noni fruit juice has been utilized in traditional medicine to have health-improving properties. According to claims, Noni fruit has hepatoprotective, antibacterial, antiviral, antifungal, antitumor, analgesic, anti-inflammatory, anti-oxidant, and immune-enhancing properties (Reem et al., 2017). It has been shown to be effective against minimizing the symptoms of lifestyle-related diseases such as atherosclerosis, hypertension and other vascular disorders, stroke and diabetes (Mandukhail et al., 2010).

Excellent antioxidant activity in Noni juice may be due to the chemical composition such as flavonoids and tannins which may protect people from the harm caused by oxygen free radicals and lipid peroxidation (Mani et al., 2014). Studies have reported that *Morinda Citrifolia*, possess vasodilatory, antioxidant, antitumor and Angiotensin Converting Enzyme inhibitor activities (Mandukhail et al., 2010), protection against systemic inflammation, aid weight management and maintenance of blood pressure through reduction in the activities of pro-degenerative markers (West et al., 2018). Enzymes called histone deacetylases (HDAC), strip acetyl groups from lysine residues in the histones' tail region. It is a transcriptional factor and epigenetic gene regulator. HDACs control the expression of oncogenes, tumor suppressors, and inflammatory genes as well as the modification of chromatin architecture (de Ruijter et al., 2003). HDAC2 specifically, is an important regulatory mechanism mediating cardiovascular regeneration which helps in gene expression by forming transcription receptor complexes (Garmis et al., 2022).

Thus, this study aimed to investigate the effect of noni fruit on the expression of a major epigenetic factor and cardiac inflammatory markers in BPA-induced toxicity of male Wistar rats.

2. Materials and methods

2.1. Animals grouping

The study was carried out in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals and was approved by the Ethical Review Committee, University of Ilorin, Ilorin, Nigeria (UERC/ASN/2018/357).

Twenty-four male Wistar rats, 5 weeks old weighing between 120 ± 5 g were obtained from the animal house of the College of Health Sciences, University of Ilorin (Ilorin, Nigeria). The rats were fed ad libitum with standard rat chow and had unlimited access to tap water. After a week of acclimatization, the animals were randomly assigned to four

groups ($n = 6$ rats/group). Rats were maintained in the animal house under environmental conditions of temperature ($22\text{--}26^\circ\text{C}$), relative humidity (50–60 %) and 12-h dark/light cycle.

2.2. Noni aqueous extract preparation

Fresh ripe fruits of *Morinda Citrifolia* (Noni fruit) (Fig. 1) were procured from a reputed herb supplier. 500 g of the fruit were ground in an electronic blender. 500mls of sterile water were added to this pulp and the mixture was soaked for 48 h, at room temperature. The slurry was filtered using filter paper (Whatman®). The filtrated extract was concentrated in a rotary evaporator under reduced pressure at 55°C (Inada et al., 2020).

2.3. Phytochemical screening

The phytochemical screening of Noni aqueous extract, as shown in Table 1, was carried out according to the method reported by Okafor and Ezejindu (2014).

2.4. Toxicity study of Bisphenol A

Bisphenol A was purchased from Bridge Biotech Laboratory, Ilorin, Kwara State. Toxicity study of Bisphenol A was carried out in a pilot study of some sample rats and a median lethal dose (LD_{50} ; the value at which 50 % of the drugs given is lethal) of 8.4 g/kg body weight of BPA was obtained when administered orally. This was carried out at Manzanita Research Laboratories, Tanke Ilorin, Kwara State according to the methods of Jayanti and Shripad (2012). For the purpose of this study, Bisphenol A in its solid powdery form was suspended in olive oil and given orally at a final concentration of 7 g/kg.

2.5. Treatment

After a week of acclimatization, the grouped animals were treated as follows: Group1 (Control) rats was fed with standard chow (CTR), Group 1: Control (Ctr: normal chow + vehicle: Olive oil), Group 2: Bisphenol A (7 g/kg, orally), Group 3: Noni aqueous extract (NAE:500 mg/kg; orally) (Chong et al., 2019) and Group 4: NAE: (500 mg/kg + BPA: 7 g/kg orally) for six weeks.

2.6. Collection of blood sample

After six weeks of treatment, animals were anesthetized with 0.8 mg Phenobarbitone intraperitoneally (50 mg/kg ip) and blood was collected



Fig. 1. A diagram showing *Morinda Citrifolia* (Noni fruit).

Table 1
Phytochemical composition of *Morinda Citrifolia* (Noni) fruit.

Chemical compound	Noni Aqueous Extract	Composition (Mg/l)
Flavonoids	+	15.0831
Tannins	+	8.4081
Glycoside	-	-
Phenol	+	0.3749
Terpenoids	-	-
Alkaloids	-	-
Saponins	-	-
Triterpenoids	-	-
Phytate	+	13.9189

–: absence; +: presence.

by cardiac puncture. Blood was collected by cardiac puncture into heparinized tube and was centrifuged at 3000 rpm for 5 min at room temperature. Plasma was stored frozen until needed for biochemical assay.

2.7. Preparation of cardiac tissue homogenates

After dissection, the heart was excised, cleared of adhering connective tissues, blotted, and weighed. After weighing, 100 mg of tissue was carefully removed, homogenized in phosphate-buffered solution (PBS) with a glass homogenizer, and centrifuged at 10,000 rpm for 10 min at 4 °C and the supernatant was collected and stored frozen until required for biochemical assays.

2.8. Determination of plasma and cardiac lipoprotein a and adenosine

Plasma and cardiac Lp(a) and adenosine were determined using ELISA kit obtained from Elabscience (Wuhan, China).

2.9. Determination of plasma and cardiac lipid peroxidation

Malondialdehyde (MDA) a marker for lipid peroxidation, was determined from the plasma and cardiac homogenate by standard non-enzymatic spectrophotometric method using assay kits from Randox Laboratory Ltd. (Co. Antrim, UK).

2.10. Determination of plasma and cardiac pro-inflammatory markers (Uric acid and TNF- α)

Plasma and cardiac uric acid were determined by non-enzymatic colorimetric method using assay kits from Randox Laboratory Ltd. (Co. Antrim, UK) and following the manufacturers' procedures. TNF- α was determined by the quantitative standard sandwich ELISA technique using monoclonal antibody specific for this parameter with kits obtained from Elabscience Biotechnology Inc. (Wuhan, China).

2.11. Determination of plasma and cardiac nitric oxide

The plasma and cardiac nitric oxide were determined by rats ELISA kits obtained from Elabscience Biotechnology Inc. (Wuhan, China) and following the manufacturers' procedures.

2.12. Determination of transcriptional marker (HDAC)

The plasma and cardiac level of HDAC was determined using Rat HDAC2 ELISA kit (Cat number ELK7409) obtained from ELK Biotechnology (Wuhan, China) in compliance with the manufacturer's procedure.

2.13. Statistical analysis

The data was presented as Means $\pm$ SEM for all of the variables. SPSS

statistical software was used to carry out statistical analysis of the data. One-way ANOVA was used to compare the mean values of variables among the groups and Bonferroni's test was used for post hoc analysis. The p-value ($P < 0.05$) was used to determine Significant differences.

3. Results

3.1. Phytochemical screening of *Morinda Citrifolia* (Noni) fruit

Effect of NAE on Body weight, Feed and Water Intake in normal and BPA administered male Wistar rats.

Administration of Bisphenol A caused an increase in body weight and feed intake compared to those administered NAE. Upon administration of Noni + BPA, there was an observable decrease in body weight compared to the animals given BPA only. Groups administered Noni showed a decrease in feed intake compared to control as shown in (Table 2).

3.2. Effect of NAE on plasma and cardiac HDAC and nitric oxide levels in normal and BPA administered male Wistar rats

There was a significant increase in plasma and cardiac HDAC levels, cardiac HDAC levels in rats administered NAE showed about 58 % increase when compared with control group. Bisphenol A administration showed a significant reduction in plasma and cardiac HDAC level when compared with control groups. On the other hand, administration of the Bisphenol caused a significant elevation in HDAC levels when compared with the control.

Plasma and cardiac Nitric oxide increased significantly in the Noni group and rats administered Bisphenol A showed decrease when compared with the control groups. The administration of Noni + BPA showed significant elevation in cardiac Nitric oxide when compared to the control and Bisphenol groups (Fig. 2).

3.3. Effect of NAE on plasma and cardiac adenosine and TG levels in normal and BPA administered male Wistar rats

Plasma and cardiac adenosine were elevated significantly in the Noni groups and decreased on administration of Bisphenol A when compared to the rats in the control group. BisphenolA + Noni showed significant elevation in Adenosine levels compared to animals administered BPA only. Noni fruit administration was shown to cause a decrease in plasma and cardiac TG when compared to control. BPA caused a two-fold increase in plasma and cardiac TG when compared to control. On administration of Noni with BPA, there was a decrease in TG when compared to animals administered BPA only (Fig. 3).

3.4. Effect of NAE on plasma and cardiac lipoprotein a and TNF alpha levels in normal and BPA administered male Wistar rats

There was an observable reduction of Lp(a) in animals administered Noni, BPA was shown to cause a significant increase in both plasma and cardiac Lp(a) when compared to control. Plasma Lp(a) was reduced in BPA + Noni group when compared with the BPA only.

BPA caused increase in plasma and cardiac TNF alpha levels and

Table 2
Body weight, feed and water intake comparison across groups.

Parameters	Control	BPA	Noni	Noni + BPA
Body weight(g)	187.8 $\pm$ 10.9	176 $\pm$ 8.2	171 $\pm$ 8.6	164 $\pm$ 6.1
Feed Intake (g)	97.86 $\pm$ 10.22	90.93 $\pm$ 8.682	77.50 $\pm$ 10.78*#	74.57 $\pm$ 8.190*#
Water Intake (ml)	248.6 $\pm$ 8.2	233.2 $\pm$ 31.9	229.3 $\pm$ 32.3	225.7 $\pm$ 31.1

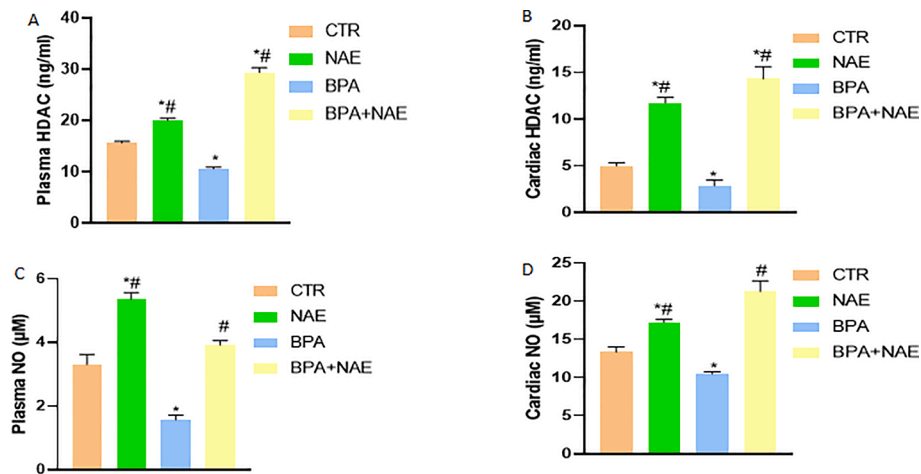


Fig. 2. Effect of Noni aqueous extract on plasma and cardiac HDAC and Nitric oxide (NO) in normal and Bisphenol A (BPA) administered animals. (* $p < 0.05$ vs CTR, # $p < 0.05$ vs BPA, CTR- control, BPA-Bisphenol A). Data were analyzed by one-way ANOVA followed by Bonferroni's Post hoc test. Values are expressed as mean $\pm$ SEM of 6 rats per group and $P < 0.05$ was taken as statistically significant.

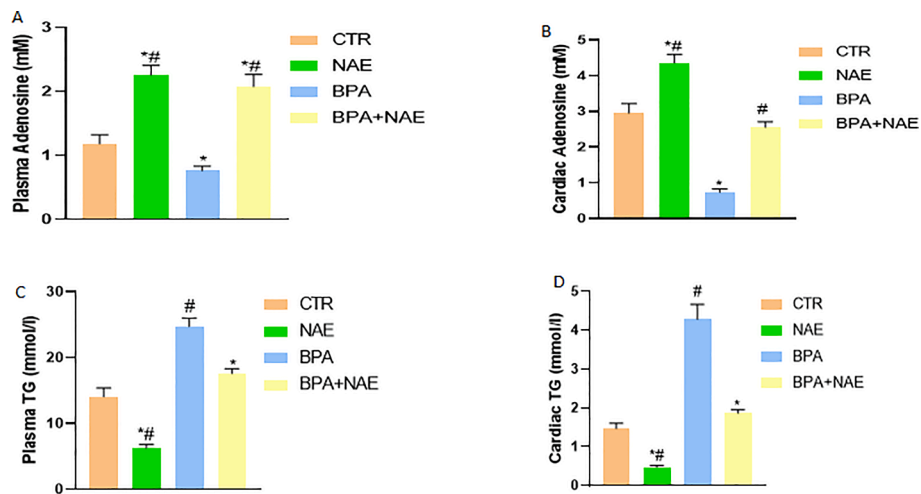


Fig. 3. Effect of Noni aqueous extract on plasma and cardiac Adenosine and Triglyceride (TG) in normal and Bisphenol A (BPA) administered animals. (* $p < 0.05$ vs CTR, # $p < 0.05$ vs BPA, CTR- control, BPA-Bisphenol A). Data were analyzed by one-way ANOVA followed by Bonferroni's Post hoc test. Values are expressed as mean $\pm$ SEM of 6 rats per group and $P < 0.05$ was taken as statistically significant.

there were significant decrease TNF alpha levels in the noni groups when compared to the control. BPA + Noni decreased TNF alpha when compared to o the rats administered BPA only (Fig. 4).

3.5. Effect of NAE on plasma and cardiac uric acid and MDA levels in normal and BPA administered male Wistar rats

Plasma and cardiac Uric acid increased significantly in the BPA groups. However, there was a decrease in Uric acid levels in the Noni group when compared to control. Groups administered BPA + Noni showed decrease uric acid levels. Furthermore, Plasma and cardiac MDA increased in BPA groups when compared with the control and noni groups. However, a slight decrease in MDA was observed in rats administered noni when compared to control (Fig. 5).

4. Discussion

The result from the study showed that Bisphenol A reduced plasma and cardiac HDAC, NO and adenosine levels and increased TG, Lp(a), TNF alpha, uric acid, MDA levels. However, administration of noni fruit had cardioprotective roles by elevating HDAC, NO and adenosine levels

and decrease in TNF alpha, Uric acid and MDA levels. It was observed that Noni fruit expressed great antioxidant activity. Studies has shown that acute or chronic exposure to BPA leads to cardiovascular, coronary, and peripheral artery disorders (Bahey et al., 2019).

According to previous studies, oxidative damage has a significant role in the development of coronary artery disease (CAD). BPA's effects on estrogenic receptors, changes in the expression of cardiac Ca²⁺-handling proteins, ion channel inhibition/activation, oxidative damage, the generation of free radicals and changes to the genome and transcriptome could all lead to cardiotoxicity. BPA is a pollutant that induces different health problems including metabolic disorders, hormonal-based tumors, and cardiovascular diseases (Mohamed et al., 2022).

From studies, humans with greater urinary BPA concentrations seemed to be more susceptible to heart disease (Melzer et al., 2010). Nitric oxide (NO) is a potent vasodilator and reduction in NO levels contributes to oxidative stress and oxidative stress has been implicated in cardiometabolic disturbances and usually causes damage to cellular structures resulting in loss of functionality (Oyabambi et al., 2019a). Studies suggests that oxidative stress, fibrosis, and apoptosis play important roles in BPA-related toxicity (Mohamed et al., 2022). In this study, BPA reduced the levels of MDA and NO showing that BPA

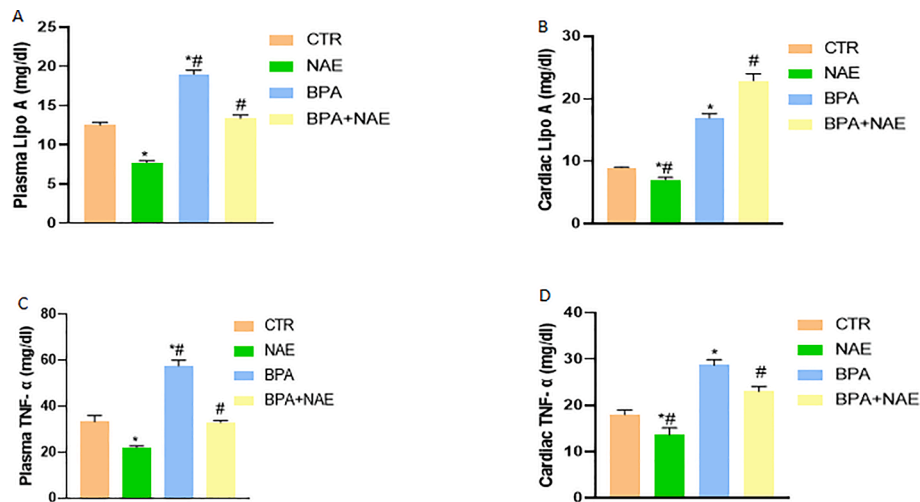


Fig. 4. Effect of Noni aqueous extract on plasma and cardiac Lp(a) and TNF- α in normal and Bisphenol A (BPA) administered animals. (* $p < 0.05$ vs CTR, # $p < 0.05$ vs BPA, CTR- control, BPA-Bisphenol A). Data were analyzed by one-way ANOVA followed by Bonferroni's Post hoc test. Values are expressed as mean $\pm$ SEM of 6 rats per group and $P < 0.05$ was taken as statistically significant.

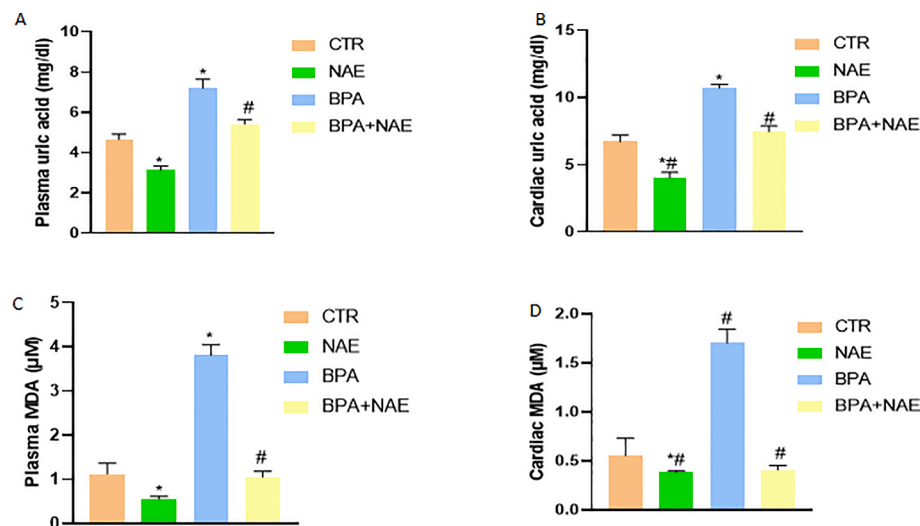


Fig. 5. Effect of Noni aqueous extract on plasma and cardiac Uric acid and Malondialdehyde (MDA) in normal and Bisphenol A (BPA) administered animals. (* $p < 0.05$ vs CTR, # $p < 0.05$ vs BPA, CTR- control, BPA-Bisphenol A). Data were analyzed by one-way ANOVA followed by Bonferroni's Post hoc test. Values are expressed as mean $\pm$ SEM of 6 rats per group and $P < 0.05$ was taken as statistically significant.

enhances oxidative stress and promotes cardiac toxicity.

Dyslipidemia is one of the major risk factors for cardiovascular disease (CVD) (Hedayatnia et al., 2020). Prevention of dyslipidemia is a key priority to effectively control the development of atherosclerosis and CVD events. Endocrine-disrupting chemicals promotes metabolic disorders including dyslipidemia and BPA has the potential to induce lipid abnormalities. Studies has shown that BPA increases the circulating levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and decrease the levels of high-density lipoprotein cholesterol (HDL-C) (Bin et al., 2020). Hypercholesterolemia is associated with the development of atherosclerosis which occurs as result of accumulation of LDL-C (Oyabambi et al., 2019b). Lipid lowering therapies reduces cholesterol and atherosclerotic burden in individuals with high risk of cardiovascular disease (Chin et al., 2018; Gerald et al., 2020). Consequent with this study, BPA showed an increase in plasma and cardiac TG, and Lp(a) level. Lipoprotein A is a low-density lipoprotein (LDL) and one of the most important single independent predictors of cardiovascular risk. It is a genetically determined risk factor for atherosclerosis, coronary artery disease, stroke and

thrombosis. Furthermore, from this study, animals administered Noni fruit showed decreased levels of TG and Lp(a) showing that *Morinda Citrifolia* has antilipemic effects. *Morinda Citrifolia* has been considered useful in cardiovascular diseases particularly in atherosclerosis and dyslipidemia (Mandukhail et al., 2010). *Morinda Citrifolia* was shown to contain increased level of phythate and flavonoids which can be attributed to its antilipemic effect, causing a decrease in triglycerides and LDL thereby improving lipid metabolism. It is established from studies that flavonoids have great cardioprotective effects. Flavonoids reduce vascular disease risks, blood pressure and as well shows antioxidant and anti-inflammatory activities (Popiolek-kalisz and Fornal, 2022).

This study showed that BPA increased TNF- α , uric acid and promotes cardiotoxicity. It also enhances the expression of TNF- α , a pro-degenerative marker. Human heart failure has long known to be associated with elevated levels pro-inflammatory cytokine TNF- α (Schumacher and Naga 2018) and also a mediator of hypertrophy (Dunlay et al., 2008). Increased Uric acid levels have been associated with a significant increase in the risk of hypertension, metabolic syndrome, and

cardiovascular disease (CVD) (Claudio and Federica, 2021). Hyperuricemia enhances the production of reactive oxygen species (ROS) which leads to the activation of inflammatory signaling pathways causing inflammation and the development of atherosclerotic lesions. Uric acid accumulation increases the production of inflammatory cytokines and promotes tissue injury. It also triggers endothelial dysfunction and oxidative stress in the cardiac tissue as a result of ROS production which affects cardiovascular health (Kimura et al., 2021; Gjin, 2018). BPA reduces expression of antioxidant enzymes which may promote oxidative stress (Abou El-Naga et al., 2022). Noni aqueous extract showed antioxidative properties which can be associated with the Tannin composition found in the fruit. Tannins enhance endothelial nitric oxide synthase activation and helps in scavenging ROS and free radicals preventing oxidative stress and promotes cardiac protection (Sieniawska, 2015).

In this study, noni fruit increased HDAC2 and adenosine levels showing that it has protective effects on cardiac functions and BPA on the other hand caused a reduction in HDAC. Adenosine plays a critical role in regulating cardiac function, including heart rate, contractility, and coronary flow (Mustafa et al., 2009). HDACs are involved in the gene expression reprogramming in multiple biological processes. It also plays significant role in vascular cell homeostasis (Yang et al., 2015). From this study, administration of *Morinda Citrifolia* increased HDAC 2 significantly and showed a double fold increase in animals treated

alongside with Bisphenol A (Fig. 6). HDAC 2 is a key regulator of heart development and controls epigenetic modification against cardiac hypertrophy. It is a great therapeutic target for the treatment of pathological conditions like CVD (Wang et al., 2021). The expression of HDAC 2 attenuates cardiac fibrosis and improves cardiovascular functions (Trivedi et al., 2007). Cardiovascular fibrosis and hypertrophy, heart failure, ischemia, energy metabolism, and contractility and relaxation are all improved by HDAC. It has been demonstrated that HDAC 2 prevent cardiac hypertrophy by binding to and preventing the transcriptional activation of myocyte enhancer factor 2 (MEF2). MEF2 is shown to activate phosphorylation signaling cascades in the formation of cardiac hypertrophy and is elevated in response to pathological stress on the heart (Justine and Bradley, 2020). Our study showed that *Morinda Citrifolia* has a major effect on HDAC2, a major downstream signaling molecule and strong transcriptional factor in cardiac programming.

5. Conclusion

In conclusion, *Morinda Citrifolia* promotes the expression of HDAC 2 activities, an epigenetic and transcriptional marker that helps modulate cardiac hypertrophy and heart failure and thereby helps to attenuate cardiotoxicity and BPA enhanced cardiac dysfunction. *Morinda Citrifolia* also ameliorated atherosclerotic cardiovascular and degenerative

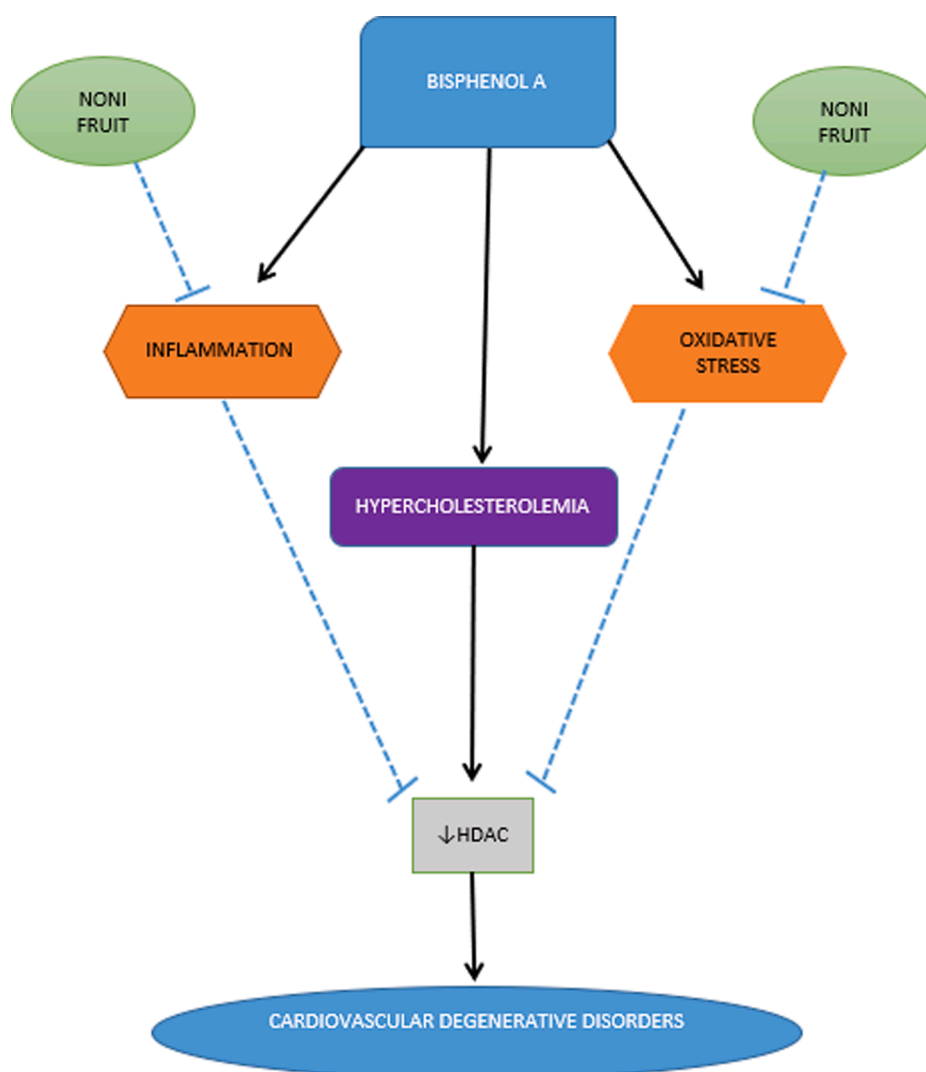


Fig. 6. Graphical abstract showing BPAs effect on cardiotoxicity and Noni's proposed mechanism of action.

disorders through reduced proinflammatory markers and oxidative stress activities.

Limitation of the study

The limitations of the study include but not limited to the toxicity nature of Bisphenol A which might not have allowed for the use of high doses of the drugs to assess for a more severe effect on the animals. Also, a histological section plus or minus might have been to add to the pool of evidences provided in the study if done but this also has limitation of over reporting and under reporting in most cases.

Ethics statement

The study was carried out in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals and was approved by the Ethical Review Committee, University of Ilorin, Ilorin, Nigeria (UERC/ASN/2018/357).

CRediT authorship contribution statement

Adewumi Oluwafemi Oyabambi: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Blessing Boluwatife Aindero:** . **Boluwatife Eunice Fashetan:** . **Kofoworola Tinuola Oni:** .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgment

The authors acknowledged the technical support of HOPE Cardiometabolic Research Team and Mr. Adebawale of Bridge Biotech is also appreciated for the laboratory analysis.

References

- Abou El-Naga, H. M. H., El-Hashash, S. A., Yasen, E. M., Leporatti, S., & Hanafy, N. A. N. (2022). Starch-based hydrogel nanoparticles loaded with polyphenolic compounds of moringa oleifera leaf extract have hepatoprotective activity in bisphenol A-induced animal models. *Polymers*, 14(14), 2846. <https://doi.org/10.3390/polym14142846>
- Bahey, N. G., Abd Elaziz, H. O., & Elsayed Gadalla, K. K. (2019). Potential toxic effect of bisphenol A on the cardiac muscle of adult rat and the possible protective effect of omega-3: A histological and immunohistochemical study. *Journal of Microscopy and Ultrastructure*, 7(1), 1–8. https://doi.org/10.4103/JMAU.JMAU_53_18
- Bhatnagar, A. (2017). Environmental Determinants of Cardiovascular Disease. *Circulation Research*, 121, 162–180. <https://doi.org/10.1161/CIRCRESAHA.117.306458>
- Bin, W., Shuangyuan, W., Zhiyun, Z., Yuhong, C., Yiping, X., Mian, L., et al. (2020). Bisphenol A exposure in relation to altered lipid profile and dyslipidemia among Chinese adults: A repeated measures study. *Environmental Research*, 184, Article 109382. <https://doi.org/10.1016/j.envres.2020.109382>
- Chin, X. T., Gun, H. C., Hazilawati, H., & Hasanah, M. G. (2018). Effect of virgin avocado oil on diet induced hypercholesterolemia in rats via ¹H NMR-based metabolomics approach. *Phytotherapy research*, 32(11), 2264–2274. <https://doi.org/10.1002/ptr.6164>
- Chong, C. L., Hussan, F., & Othman, F. (2019). Hepatoprotective effects of morinda citrifolia leaf extract on ovariectomized rats fed with thermoxidized palm oil diet: evidence at histological and ultrastructural level. *Oxidative Medicine and Cellular Longevity*, 19, 1–10. <https://doi.org/10.1155/2019/9714302>
- Choo, Y. X., Teh, L. K., & Tan, C. X. (2023). Effects of sonication and thermal pasteurization on the nutritional, antioxidant, and microbial properties of noni juice. *Molecules*, 28, 313. <https://doi.org/10.3390/molecules28010313>
- Claudio, B., & Federica, P. (2021). Uric acid and risk of cardiovascular disease: A question of start and finish. *Hypertension*, 78, 1219–1221. <https://doi.org/10.1161/HYPERTENSIONAHA.121.17631>
- de Ruijter, A. J., van Gennip, A. H., Caron, H. N., Kemp, S., & van Kuilenburg, A. B. (2003). Histone deacetylases (HDACs): Characterization of the classical HDAC family. *The Biochemical journal*, 370(Pt 3), 737–749. <https://doi.org/10.1042/BJ20021321>
- Dunlay, S. M., Weston, S. A., Redfield, M. M., Killian, J. M., & Roger, V. L. (2008). Tumor necrosis factor-alpha and mortality in heart failure: A community study. *Circulation*, 118(6), 625–631. <https://doi.org/10.1161/CIRCULATIONAHA.107.759191>
- Erbaş, O., Altuntaş, İ., Çağlar, Ö., Özyılmaz, E., Sari, E., Üzümcü, İ. et al. (2022). Experimental Model of Cardiotoxicity. Risk Factors for Cardiovascular Disease. *IntechOpen*, <https://doi.org/10.5772/intechopen.101401>.
- Fenichel, P., Chevalier, N., & Brucker-Davis, F. (2013). Bisphenol A: An endocrine and metabolic disruptor. *Annales d'Endocrinologie*, 74(3), 211–220. <https://doi.org/10.1016/j.ando.2013.04.002>
- Fonseca, M. I., Lorigo, M., & Cairrao, E. (2022). Endocrine-disrupting effects of bisphenol A on the cardiovascular system: A review. *Journal of xenobiotics*, 12(3), 181–213. <https://doi.org/10.3390/jox12030015>
- Gao, X., & Wang, H. S. (2014). Impact of bisphenol a on the cardiovascular system - epidemiological and experimental evidence and molecular mechanisms. *International Journal of Environmental Research and Public Health*, 11(8), 8399–8413. <https://doi.org/10.3390/ijerph110808399>
- Garmis, N., Damaskos, C., Dimitroulis, D., Kouraklis, G., Garmis, A., Sarantis, P., et al. (2022). Clinical significance of the histone deacetylase 2 (HDAC-2) expression in human breast cancer. *Journal of Personalized Medicine*, 12(10), 1672. <https://doi.org/10.3390/jpm12101672>
- Gerald, F. W., Alberico, L. C., Luis, M., Alberto, Z., Pi, A., & Lale, T. (2020). Hypercholesterolemia and cardiovascular disease: Focus on high cardiovascular risk patients. *Atherosclerosis Supplements*, 42, 30–34. <https://doi.org/10.1016/j.atherosclerosis.2021.01.006>
- Gjin, N. (2018). Uric acid and cardiovascular disease. *Clinica Chimica Acta*, 484, 150–163. <https://doi.org/10.1016/j.cca.2018.05.046>
- Hedayatnia, M., Asadi, Z., Zare-Feyzabadi, R., Yaghoobi-Khorasani, M., Ghazizadeh, H., Ghaffarian-Zirak, R., et al. (2020). Dyslipidemia and cardiovascular disease risk among the MASHAD study population. *Lipids in Health and Disease*, 19(1), 42. <https://doi.org/10.1186/s12944-020-01204-y>
- Ilkun, O., & Boudina, S. (2013). Cardiac dysfunction and oxidative stress in the metabolic syndrome: An update on antioxidant therapies. *Current Pharmaceutical Design*, 19(27), 4806–4817. <https://doi.org/10.2174/1381612811319270003>
- Inada, A. C., Silva, G. T., Silva, L. P., Alves, F. M., Filiú, W. F., Asato, M. A., et al. (2020). Therapeutic effects of *Morinda citrifolia* Linn. (Noni) aqueous fruit extract on the glucose and lipid metabolism in high-fat/high-fructose-fed swiss mice. *Nutrients*, 12(11), 3439. <https://doi.org/10.3390/nu12113439>
- Jayanti, P., & Shripad, B. D. (2012). Acute toxicity of Bisphenol A in rats. *Indian Journal of Experimental Biology*, 50, 425–429.
- Justine, S.H. & Bradley, S.F. (2020). Chapter 13 - Histone modification as a potential preventative and therapeutic approach for cardiovascular disease. *Academic Press*, 20, 337–359. <https://doi.org/10.1016/B978-0-12-816422-8.00014-3>
- Kimura, Y., Tsukui, D., & Kono, H. (2021). Uric acid in inflammation and the pathogenesis of atherosclerosis. *International Journal of Molecular Sciences*, 22(22), 12394. <https://doi.org/10.3390/ijms222212394>
- Leslie, H. A., van Velzen, M. J., Brandsma, S. H., Vethaak, A. D., Garcia-Vallejo, J. J., & Lamoree, M. H. (2022). Discovery and quantification of plastic particle pollution in human blood. *Environment International*, 163, Article 107199.
- Mandukhail, S. U., Aziz, N., & Gilani, A. H. (2010). Studies on antidiabetic effects of *Morinda citrifolia* (Noni) fruit, leaves and root extracts. *Lipids in Health and Disease*, 9, 88. <https://doi.org/10.1186/1476-511X-9-88>
- Mani, S., Ram, B. R., Kuldeep, D., Babu, L., Subramaniyam, S., Gopikunte, J. R., et al. (2014). Effect of *Morinda citrifolia* (Noni) fruit juice on antioxidant, hematological and biochemical parameters in N-methyl-N-nitrosourea (NMU) induced mammary carcinogenesis in sprague-dawley rats. *International Journal of Pharmacology*, 10, 109–119. <https://doi.org/10.3923/ijp.2014.109.119>
- Melzer, D., Rice, N. E., Lewis, C., Henley, W. E., & Galloway, T. S. (2010). Association of urinary bisphenol a concentration with heart disease: Evidence from NHANES 2003/06. *PLoS One*, 5(1), e8673.
- Mohamed, M.B., Mohsen, M.E., Gehad, E.E., Asmaa, E.E., Mohammad Abd-El-Same'e, E., Mohamed, G.H., Fatemah, H.A. & Alaa, F. (2022). Potential Effects of Bisphenol A on the Heart and Coronary Artery of Adult Male Rats and the Possible Role of L-Carnitine. *Journal of Toxicology*, 2022, 1–14. <https://doi.org/10.1155/2022/7760594>
- Mustafa, S. J., Morrison, R. R., Teng, B., & Pelleg, A. (2009). Adenosine receptors and the heart: Role in regulation of coronary blood flow and cardiac electrophysiology. *Handbook of Experimental Pharmacology*, 193, 161–188. https://doi.org/10.1007/978-3-540-89615-9_6
- Okafor, I. A., & Ezejindu, D. N. (2014). Phytochemical studies on *Portulaca oleracea* (purslane) plant. *G.J.B.A.H.S.*, 3(1), 132–136.
- Okugbe, E., Ohore, & Songhe, Z. (2019). Endocrine disrupting effects of bisphenol A exposure and recent advances on its removal by water treatment systems. A review. *Scientific African*, 5, e00135. <https://doi.org/10.1016/j.sciaf.2019.e00135>
- Oyabambi, A.O., Areola, E., Olatunji, L.A., & Soladoye, A.O. (2019a). Uric acid is a key player in salt-induced endothelial dysfunction: the therapeutic role of *Stigma maydis* (corn silk) extract. *Applied Physiology, Nutrition, and Metabolism*, 45(1), 67–71. Published by National Research Council of Canada. Available online <http://www.nrcresearchpress.com>.
- Oyabambi, A. O., Salam, B. S., Erdoo, A., & Zainab, O. (2019b). Role of high-density lipoprotein in the ameliorative activity of *Bryophyllum pinnatum* in male Wistar rats fed a high fat diet. *LASU Journal of Medical Sciences*, 4(2), 38–43.
- Popiolek-Kalisz, J., & Fornal, E. (2022). The impact of flavonols on cardiovascular risk. *Nutrients*, 14(9), 1973. <https://doi.org/10.3390/nu14091973>
- Reem, A. A., Yusrida, D., Ibrahim, M. A., Arshad, A., Lim, V., & Laghari, M. H. (2017). *Morinda citrifolia* (Noni): A comprehensive review on its industrial uses,

- pharmacological activities, and clinical trials. *Arabian Journal of Chemistry*, 10(5), 691–707. <https://doi.org/10.1016/j.arabjc.2015.06.018>
- Schumacher, S. M., & Naga, S. V. (2018). Tumor necrosis factor- α in heart failure: An updated review. *Current Cardiology Reports*, 20(11), 117. <https://doi.org/10.1007/s11886-018-1067-7>
- Sieniawska, E. (2015). Activities of tannins – from in vitro studies to clinical trials. *Natural Product Communications*, 10(11), 1877–1884.
- Trivedi, C. M., Luo, Y., Yin, Z., Zhang, M., Zhu, W., Wang, T., et al. (2007). Hdac2 regulates the cardiac hypertrophic response by modulating Gsk3 beta activity. *Nature Medicine*, 13(3), 324–331.
- Vaduganathan, M., Mensah, G. A., Turco, J. V., Fuster, V., & Roth, G. A. (2022). The global burden of cardiovascular diseases and risk: A compass for future health. *Journal of the American College of Cardiology*, 80(25), 2361–2371. <https://doi.org/10.1016/j.jacc.2022.11.005>
- von Goetz, N., Wormuth, M., Scheringer, M., & Hungerbühler, K. (2010). Bisphenol a: How the most relevant exposure sources contribute to total consumer exposure. *Risk Analysis*, 30(3), 473–487. <https://doi.org/10.1111/j.1539-6924.2009.01345.x>
- Wang, Z., Zhao, Y. T., & Zhao, T. C. (2021). Histone deacetylases in modulating cardiac disease and their clinical translational and therapeutic implications. *Experimental Biology and Medicine*, 246(2), 213–225. <https://doi.org/10.1177/1535370220944128>
- West, B. J., Deng, S., Isami, F., Uwaya, A., & Jensen, C. J. (2018). The potential health benefits of noni juice: A review of human intervention studies. *Foods (Basel, Switzerland)*, 7(4), 58. <https://doi.org/10.3390/foods7040058>
- Yang, J. Y., Wang, Q., Wang, W., & Zeng, L. F. (2015). Histone deacetylases and cardiovascular cell lineage commitment. *World Journal of Stem Cells*, 7(5), 852–858. <https://doi.org/10.4252/wjsc.v7.i5.852>