The Journal of Phytopharmacology 2020; 9(5): 323-328
Online at: www.phytopharmajournal.com

Research Article

ISSN 2320-480X
JPHYTO 2020; 9(5): 323-328
September- October
Received: 24-07-2020
Accepted: 15-09-2020
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doi: 10.31254/phyto.2020.9506

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Evaluation of antioxidant and antidepressant activity of hydro-alcoholic extract of *Ximenia americana* stem bark

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ABSTRACT

The present study was undertaken to evaluate the antioxidant and antidepressant activity of hydro-alcoholic extract of *Ximenia americana* in case of Sodium fluoride induced toxicity on ICR mices. Antioxidant activity of the plant was evaluated *in vitro* through 2,2'-Azobis (2-Amidino-propane) Dihydrochloride test, metal chelating assay and total antioxidant capacity and *in vivo* through evaluation of malondialdehyde content in brain and liver. Antidepressant activity was evaluated through tail suspension test. *In vitro* evaluation of antioxidant activity showed that hydro-alcoholic extract of stem bark of *Ximenia americana* possesses a total antioxidant capacity of 303.081 ± 4.946 mg equivalent ascorbic acid per gram. From 2, 2'-Azobis (2-Amidino-propane) Dihydrochloride and metal chelating tests, it emerged that the extract inhibits hemolysis and chelates metals concentration-dependent manner. Animals were randomly divided into four groups with five animals in each group. The control group received distilled water, group II received sodium fluoride at dose of 13.6 mg/kg body weight, group III and group VI: received respectively hydro-alcoholic extract of *Ximenia americana* at 250 mg/kg and 500 mg/kg with sodium fluoride during 7 days. Results showed sodium fluoride decrease animal's body weight even at the presence of the extract, increased significantly animal's inactivity time and malondialdehyde levels in liver and brain. Animal's inactivity time and malondialdehyde levels were significantly improved at the presence of the hydro-alcoholic extract of *Ximenia americana*. *Ximenia americana* have potential to mitigate sodium fluoride toxicity.

Keywords: Ximenia americana, brain, antioxidant, antidepressant, sodium fluoride.

INTRODUCTION

Fluorine is toxic ubiquitous element in the environment. Due to its high reactivity, it's always found on combine form. Chronic exposition to fluorine leads to many adverse effects. Its accumulation in calcified tissues, bones and teeth leads respectively to skeletal and dental fluorosis [1, 2]. Adverse effects of fluorine are also observed in soft tissues. Acute fluoride toxicity is characterized by nausea, diarrhea, abdominal pain, vomiting, depression, cardiac arrhythmia, hypocalcemia and hyperkalemia [3, 4]. Accumulation of fluorine leads to structural changes, metabolic lesions and altered enzyme's activities in soft tissues such as brain, kidney and liver [5]. Previous studies revealed that accumulation of fluorine in brain of children lead to diminution of Intelligence Quotient (IQ) [6, 7]. Fluorine increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) leading to lipid peroxidation and lower antioxidant defense [8, 9]. Amelioration of fluoride toxicity by vitamin C, vitamin D, vitamin E and other plants extracts have shown in recent studies [10, 11, 12]. *X. americana* is a plant known to possess analgesic, antimicrobial, antibacterial, antifungal properties and used like poison's antidote and in treatment of diarrhea, fever, tuberculosis [13, 14]. Uchôa *et al.*, 2016 and Almeida *et al*., 2016 [15, 16] have shown antiradical activity of this plant *in vitro.* The present study was conduct to evaluate the antioxidant and antidepressant activity of *X. americana in vivo.*

MATERIAL AND METHODS

Animals

Manipulations were carried out on ICR mice weighing around 15–20g from Faculty of Sciences laboratory of University of Lome. They were maintained at 24 °C with free access to water and food, under a 12 h of light and 12 h of dark. The study design and experimental protocols were in accordance with institutional guidelines and ethics of Laboratory of Physiology/Pharmacology of University of Lome-Togo (ref: 0001/2012/CB-FDS-UL).

Plant material

The stem bark of *Ximenia americana* L. (Olacaceae) was collected at Oubiog, 20 km of Dapaong (Togo). The plant was identified and a specimen was deposited on number TG 15213 in herbarium of Botany Laboratory of Lome University.

Preparation of the extract

X. americana L. stem bark was reduced in small pieces after washing, dried at 20°C for one week and pulverized. About 400 g of powder were dissolved in 4l of an ethanol-distilled water mixture (70/30, V/V) and then stirred intermittently for 72 h. The mixture was filtered and the filtrate was evaporated with rotavapor Heidolph 2 to obtain 101 g of extract with yield of 25, 25%.

Phytochemical study

Phytochemical screening

Chemical groups, reducing sugars, tannins, flavonoids, saponins, carbohydrates, reducing compounds and alkaloids were explored by qualitative tests [17].

Quantitative tests

Total flavonoids content

For the determination of total flavonoids in the extract, 2 ml of aluminum chloride (20 mg/ml) and 6 ml of sodium acetate (50 mg/ml) were added to 2 ml of extract (1mg/ml) or standard (rutin). The blank was prepared with 2 ml of ethanol. After 2h30 min of incubation, the absorbance was read at 440 nm against the blank. Content of flavonoids was calculated as a rutin equivalent from the calibration curve of rutin standard solutions [18].

Determination of total phenols and tannins

The total phenols in the extract were assayed by Folin-Ciocalteu method. Total tannins determination was carried out by a second dosage of total phenols after its fixation by PVPP (polyvinylpolypyrrolidone). Total tannins were determined from the difference between absorbances of the first and second assays [19].

***In vitro* antioxidant activity of the extract**

Total antioxidant capacity

This test was carried out according to the method of Prieto *et al.,* [20]. Amounts of 0.3 ml of ascorbic acid or extract at 1 mg/ml were added to 3 ml of reagent (0.6 M sulfuric acid, 28 M sodium phosphate and 4 mM ammonium molybdate). The whole were incubated at 95 ° C for 90 min and the absorbance was read at 695 nm against the blank (0.3 ml of methanol instead of the extract). Total antioxidant capacity was determined as ascorbic acid equivalent from the calibration curve of ascorbic acid standard solutions.

Metal chelating assay

Extract and EDTA ranging from 50 to 250 µg/ml were prepared. At each concentration, 0.05 ml of $FeCl_2$ at 2 mmol/l and 0.2 ml of 5 mmol/l ferrozine were added. The whole was vigorously stirred with vortex, incubated for 10 min and absorbance was read at 562 nm [21]. The inhibition percent of ferrozine-Fe^{2+} complex calculated according to the following equation:

$$\% \text{ inhibition} = [(A_0 - A_1) / A_0] \times 100$$

A_0: Absorbance of control

A_1: Absorbance of extract or EDTA

AAPH Test (2,2-Azobis 2 Amidinopropane Dihydrochloride)

AAPH generate free radicals inducing hemolysis inhibit by antioxidants. The free radical scavenging activity of the extract was determined by the method described by Bakoma *et al*. [22].

Effect of the hydro-alcoholic extract of *X. americana* stem bark on depression

Depression was induced by sodium fluorine (NaF). The animals were ranged in four groups of 5 mices treated as follows:

Group I (control group): treated with distilled water

Group II: treated with sodium fluoride (NaF) at dose of 13.6 mg/kg body weight

Group III: treated with hydro-alcoholic extract of *X. americana* at 250 mg/kg and NaF at 13.6 mg/kg after 1h.

Group VI: treated with hydro-alcoholic extract of *X. americana* at 500 mg/kg and NaF at 13.6 mg/kg after 1h.

The animals were treated by gavage once a day for 7 days. During the treatment, the weight of the animals was taken. On the 8th day, animals were subjected to the tail suspension test.

Tail suspension test

Immobility times of the animals were determined according to the method of Steru *et al.,* [23]. Animals were suspended with adhesive at 10 cm of the support and immobility time was recorded during 6 min of suspension.

Weight of the organs

Animals were sacrificed, liver, kidneys and brain were removed and weighed. The relative weights of each organs were calculated.

Determination of malondialdehyde content

The malondialdehyde level was determined according to the method described by Misseboukpo *et al*. [24].

Statistical analyses

The results obtained were analyzed using the graphpad prism 6.02 software and the values expressed as means ± standard error. Comparisons between the values were made using ANOVA test followed by the Tukey's test. Differences between groups were considered significant at $p < 0.05$.

RESULTS

Phytochemical screening

The results of phytochemical screening are resumed in table 1.

Quantitative tests

Results of quantitative tests are resumed in table 2.

***In vitro* antioxidant activities of the extract**

Total antioxidant capacity (TAC)

Hydro-alcoholic extract of the stem bark of *X. americana* revealed an antioxidant activity in the order of 303.081 ± 4.946 mg Equivalent of Ascorbic acid/g of extract.

Metal chelating activity of *X. americana*

The metal chelating activity of the hydro-alcoholic extract of stem bark of *Ximenia americana* was performed in comparison with EDTA's activity. Extract and EDTA chelate metals concentration-dependent manner. IC_{50} comparison (table 3) shows that the chelating activity of the extract is higher than that of EDTA (Fig.1).

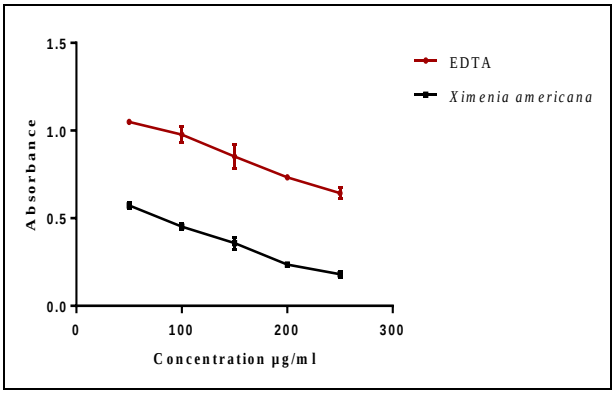


Figure 1: Curve of absorbance of the extract compared to that of EDTA.

Absorbance was read at 562 nm. Results represent mean ± SEM (n=3)

AAPH test

Hemolysis induced by AAPH was inhibited in the presence of hydro-alcoholic extract of stem bark of *X. americana* and ascorbic acid concentration-dependent manner (Fig. 2). Ascorbic acid's inhibitory activity is more important.

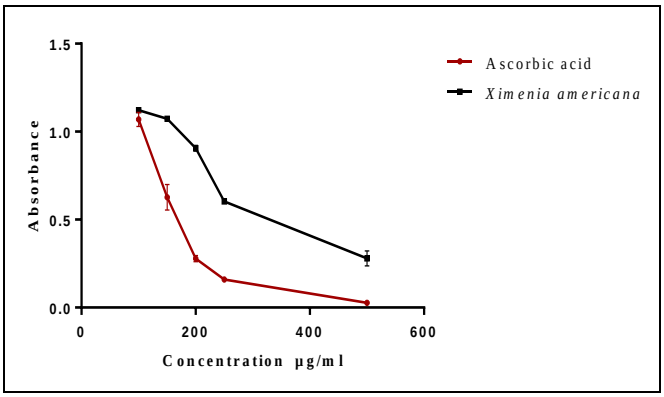


Figure 2: Curve of absorbance of extract compared to that of Ascorbic acid.

Absorbance was read at 540 nm. Results represent mean ± SEM (n=3)

Pharmacologic tests

Effect of extract on the rate of change in body weight of animals

NaF treatment resulted in a significant decrease in weight of animals ($p<0.01$) compared to control group even at presence of the extract at doses of 250 mg/kg and 500 mg/kg (Fig. 3).

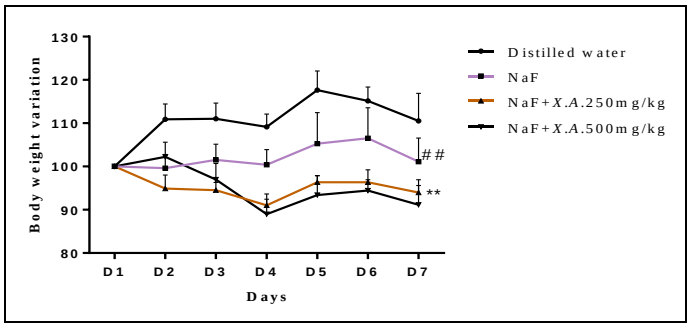


Figure 3: Effect of hydro alcoholic extract of *X. americana* on the rate of change in body weight of animals

The rate of variation of animal's weights is expressed in percentage. The weight of the first day is considered 100% and the rate is calculated with the formula: T = (P_1 × 100) / P; P = Weight at day, with P_1 = Weight at 1st day. Differences are calculated on the basis of the control group. Data were analyzed with one-way ANOVA followed by Tukey's test. The results represent the mean ± SEM (n=5). $^{\#\#}$ $p<0.01$ (NaF vs control), ** $p<0.01$ (treated vs NaF).

Effect of hydro-alcoholic extract of *X. americana* stem bark on immobility period in tail suspension test

NaF increased significantly ($p<0.05$) inactivity time of the mice compared to control group. Hydro-alcoholic extract of *X. americana* reduced this inactivity time respectively at dose of 250 mg/kg ($p<0.05$) and 500 mg/kg ($p < 0.001$) (Fig. 4).

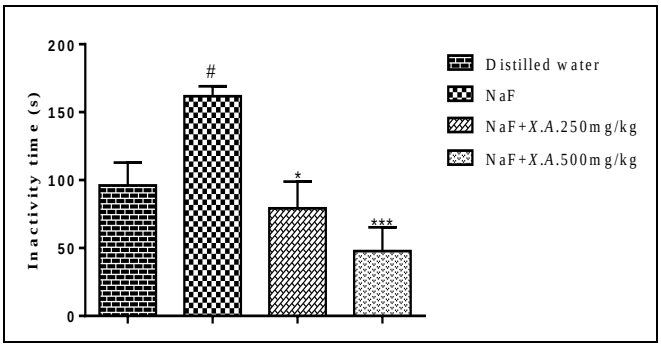


Figure 4: Effect of hydro alcoholic extract of *X. americana* on immobility time

Immobility times are expressed in second. Data were analyzed with one-way ANOVA followed by Tukey's test. The results represent the mean ± SEM (n=5). $^{\#}$ $p<0.05$ (NaF *vs* control), * $p<0.05$ (treated *vs* NaF), *** $p<0.001$ (treated *vs* NaF).

Effect of the extract on relative weights of organs

No differences were found in liver and kidney weights. But there was a significant decrease ($p<0.01$) of brain's weight in NaF treated group compared to the control. This decrease was significantly improved with the extract at 500 mg/kg ($p<0.05$) (fig. 5).

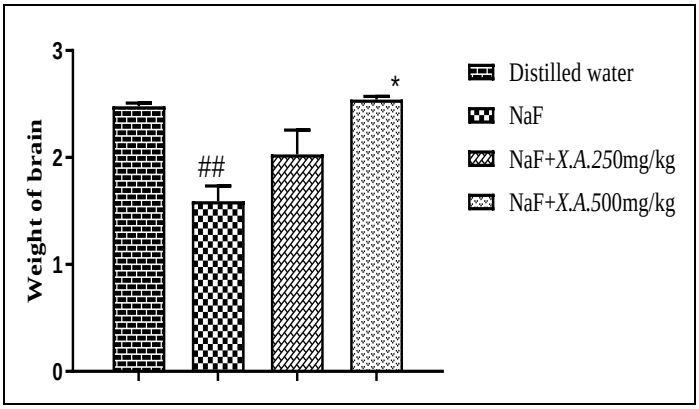
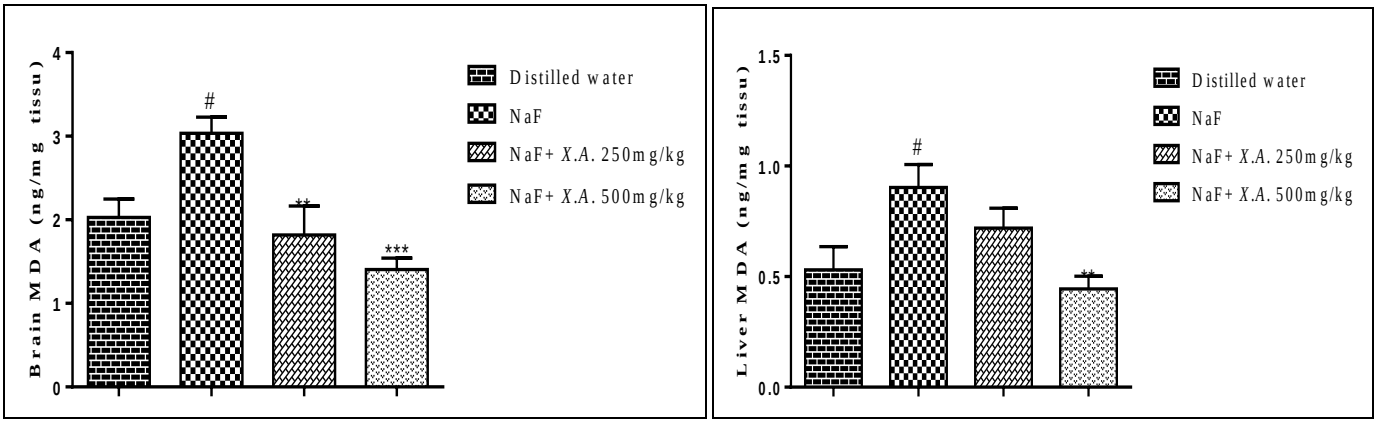


Figure 5: Effect of the extract on brain's relative weight

Relative weight of brain was expressed in grams. Data were analyzed with one-way ANOVA followed by Tukey's test. The results represent the mean ± SEM (n=5). $^{\#\#}p<0.01$ (NaF *vs* control), * $p<0.05$ (treated *vs* NaF).

Effect of the extract on lipid peroxidation in brain and liver

Lipid peroxidation in organs was assessed by the determination of MDA (malondialdehyde) content. There is a significant increase ($p<0.05$) in MDA levels in both organs in NaF exposed mice. MDA level decrease significantly in brain at the presence of extract at doses of 250 mg/kg ($p<0.01$) and 500 mg/kg ($p<0.001$). In liver, the decrease is significant only at a dose of 500 mg/kg ($p<0.01$) (Fig. 6, A and B).



A **B**

Figure 6: Effect of hydro alcoholic extract of *X. americana* on lipid peroxidation in brain (A) and liver (B).

The reaction between lipid peroxidation products (MDA) and thiobarbituric acid product TBARS complexes which absorbance is measured at 535 nm with spectrophotometer. The values are expressed as nanogram of MDA/mg of crushed tissue. The results represent the mean ± SEM (n=5). Significant differences were observed between groups, A: $^{\#}p<0.05$ (NaF *vs* control), ** $p<0.01$ (treated *vs* NaF), *** $p<0.001$ (treated *vs* NaF). B: $^{\#}p<0.05$ (NaF vs control), **$p<0.01$ (treated vs NaF) (One-way ANOVA followed by Tukey's test).

DISCUSSION

Fluoride's toxicity is linked to oxidative stress leading to diseases such as neurodegenerative diseases, diabetes and cancer. Free radicals generated in case of fluoride exposition result in lipid peroxidation, protein, DNA oxidation and alteration of endogenous antioxidants [8, 25, 26]. Soft tissues like liver, kidney and brain are affected by this mechanism. Because of its high oxygen utilization (20% of total oxygen) and its high polyunsaturated fatty acid content, the brain is probably the most affected by the damage caused by oxidative stress [27, 28].

The aim of this work was to evaluate the antioxidant and antidepressant activities of hydro-alcoholic extract of *X. americana L.* stem bark on stress induced by NaF on ICR mices. In the present study, phytochemical tests reveal the presence of reducing sugars, tannins, flavonoids, saponins, carbohydrates and reducing compounds. Quantitative tests showed 79.58 ± 0.343 mg GAE/g of total phenols in which total tannins represent 62.21% compare to 678.66 ± 2.31 mg of GAE/g in ethanolic extract [15]. The flavonoids content of the plant is in order of 27.91 ± 0.536 mg RE/g. Hydro-alcoholic extract of *X. americana L.* stem bark content high amount of polyphenols. Antioxidant potential of polyphenols is now great of interest because of its protective effect against neurodegenerative and cardiovascular diseases [29]. Antioxidant activity was evaluated through the determination of the total antioxidant capacity (TAC) which highlight all antioxidant compounds contained in the extract. This test reveals that the extract possesses an antioxidant capacity in order of 303.081 ± 4.946 mg Eq AA/g of extract. Antioxidant activity of these different compounds goes through several mechanisms, so we evaluated the metal chelating activity of the extract *in vitro* and its antiradical activity *in ex vivo* by AAPH test. Ferrous ions are powerful prooxidants that catalyze the decomposition of hydroperoxides into alkoxyl and peroxyl radicals enhancing lipid peroxidation [30], chelators of these ions can protect against oxidative damage. Extract's chelating capacity was determined by ferrozine method. Ferrozine forms with free ferrous ions a complex (ferrozine-Fe^{2+}) which is inhibited by competition in presence of chelator. Hydro-alcoholic extract of *X. americana* stem bark inhibits this complex formation concentration-dependent manner. IC_{50} comparison show that the extract possesses a strong chelating activity. Hemolysis induced by AAPH is also inhibited by the extract concentration-dependent manner. Those tests reveal extract's chelating and antiradical activities due to its content in polyphenols which may inhibit free radicals formation, interact directly with free radicals like scavengers or chelate metals involve in free radicals production such as copper, iron and zinc [30, 31].

Body weight of animals exposed to NaF decrease significantly compared to controls even at presence of the extract. This could be

explained by a lack of appetite caused by sodium fluoride. Basha and Madhusudhan [26] have shown that fluoride decrease rat's feed and water consumption. Neurotoxicity of fluoride has been discussed in various studies. It can lead to neurodegeneration, depression and decreased in Intelligence Quotient (IQ) [6, 7, 26]. Tail suspension test is one of tests which have been used in research of new antidepressant drugs, stressed animals become immobile and this immobility is correlated with a depressive state [23]. Immobility time generate by NaF is significantly reduced by hydro-alcoholic extract of *X. americana* at doses of 250 mg/kg and 500 mg/kg. The decrease of immobility time can be due to mechanism that contributes to increase concentration of monoamines such as dopamine, norepinephrine and serotonin in the brain. Extract therefore acts either by inhibiting the reuptake of these neurotransmitters or by the inhibiting monoamines oxidases [32, 33]. NaF-exposed mice exhibit a significant decrease in relative brain weight compare to control, this decrease is significantly improved by the extract at dose of 500 mg/kg. However, no differences were found in liver and kidneys weight. Decrease of brain weight of NaF treated mice show neurodegeneration induced by free radicals generated. This result confirms that the brain is the most affected organ by oxidative stress. Lipid peroxidation was evaluated *in vivo* by determination of MDA level; it showed significant increase of MDA in liver and brain of NaF-exposed mice compared to the control. This suggests that fluorine leads to production of superoxide and hydroxyl radicals that alter the antioxidant system of these organs [8, 26]. The hydro-alcoholic extract of *X. americana* at doses of 250 mg/kg and 500 mg/kg significantly decreased brain MDA content but the decrease was significant only at dose of 500 mg/kg in the liver. The extract would have increased antioxidant potential in both organs in the treated mice, which would lead to decreased lipid peroxidation. These results suggest the scavenging of free radicals or metal ions chelation or chelation of fluorine by hydro-alcoholic extract of *X. americana* stem bark. Fluorine alters antioxidant potential in animals and increase free radicals production leading to lipid peroxidation and neurodegeneration. Various studies have shown that fluorine decrease SOD, CAT and GSH-Px activities and children's IQ [6, 7, 8]. Plants polyphenols are very important family of antioxidants; they are excellent free radical scavengers [33, 34]. Xiong *et al*. in 2011 and Magalingam *et al.* in 2015 [35, 36] have demonstrated the antidepressant effect of flavonoids. *X. americana* with it contain in polyphenols could help in case of NaF toxicity.

CONCLUSION

This study shows that NaF mechanism involves oxidative stress and the brain is the most affected organ. Indeed, tail suspension test has led to conclusion that fluoride impairs central nervous system function. Damages caused by sodium fluoride was improved by hydro-alcoholic extract of *X. americana* stem bark, which revealed its neuroprotective effect by antidepressant activity. Antioxidant tests and MDA content in the liver and brain showed antioxidant activity of the extract. Antioxidant and antidepressant activities of hydro-alcoholic extract of *X. americana* stem bark may be due to the presence of polyphenols therefore *X. americana* could be used in treatment of diseases linked to oxidative stress because of its content in polyphenols.

Acknowledgments

The authors are greatfull to the Laboratory of Physiology's responsibles of Lome University to help conduce this work.

Conflict of interest

The authors declare no conflict of interests

Funding

No funding was received for this study.

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HOW TO CITE THIS ARTICLE
Togbossi LA, Lawson-Evi P, Diallo A, Eklu-Gadegbeku K, Aklikokou K. Evaluation of antioxidant and antidepressant activity of hydro-alcoholic extract of *Ximenia americana* stem bark. J Phytopharmacol 2020; 9(5):323-328.