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Aqueous Extract of *Erythrina senegalensis* Exhibits Dose-Dependent Hepatoprotective Activity on Paracetamol-Induced Liver Damage in Wistar Rats

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Abstract

Erythrina senegalensis is utilized in the treatment of liver diseases in folklore medicine in most of northern Nigeria, but sufficient pharmacological-based and peer-reviewed scientific literature is not available to authenticate its use in the treatment of liver ailments. This research is aimed at assessing the hepatoprotective effects of *Erythrina senegalensis* against paracetamol-induced (PCM-induced) hepatotoxicity in wistar albino rats. This was evaluated by estimating the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) as compared with the control group. The extract was concentrated and then desired concentrations of extracts were made by dissolving in normal saline. Four different doses of aqueous extracts *Erythrina senegalensis* (200, 300, 400 and 500 mg/kg) were administered orally for 6 consecutive days after the 72 hrs administration of paracetamol (1500 mg/kg) per body weight. Paracetamol significantly induced oxidative stress in the liver, ultimately leading to increased serum levels of liver enzyme markers like alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase. Administration of the extracts showed significant ($p < 0.05$) and dose-dependent hepatoprotective activity resulting in decrease in the activity of ALT, AST and ALP. These data revealed that *Erythrina senegalensis* aqueous extracts possess significant hepatoprotective activity against PCM-induced toxicity attributable to its constituent phytochemicals. The mechanism of hepatoprotection seems to be through the modulation of antioxidant enzyme systems.

Keywords

Hepatoprotective, *Erythrina senegalensis*, Hepatotoxicity, Paracetamol, Oxidative Stress

1. Introduction

The liver, being the centre of metabolic functions, plays an essential role in metabolizing a plethora of xenobiotics. It is therefore more vulnerable to the toxicity of these chemicals. Hepatotoxicity, either dose-related or idiosyncratic, is considered a global health concern and may occur as a result of drug metabolism. Because of the lack of effective treatment options, liver diseases have extremely poor prognosis and high mortality. Even though various advancements have been achieved in the field of modern medicine, liver diseases still remain a major health issue. In view of that, investigations into new therapeutic approaches are still ongoing [1] [2]. One of the most typical examples of dose-related toxicity is that of paracetamol [3]. Paracetamol is most commonly used as an analgesic and antipyretic, considered safe in its therapeutic doses, but overdose toxicity of paracetamol is one of the most common among the pharmaceutical product poisonings that cause liver injury. In the United States alone, it accounts for more than 50% of overdose-related acute liver failure and about 20% of the liver transplant cases [4] [5]. Metabolism of paracetamol takes place mainly in the liver, whereby it is metabolized to the more water soluble glucuronide and sulphate conjugates that are subsequently excreted via the urine. Paracetamol toxicity has been attributed to the formation of N-acetyl p-benzoquinone imine (NAPQI), a highly reactive metabolite, by the hepatic cytochrome P450. NAPQI is initially detoxified by conjugation with reduced glutathione (GSH) to form mercapturic acid. However, when the rate of NAPQI formation exceeds the rate of detoxification by GSH, it oxidizes tissue macromolecules such as lipids or thio (-SH) group of proteins and alters the homeostasis of calcium after depleting GSH [5] [6], causing damage to the macromolecules in vital biomembranes and ultimately, liver damage [7].

Complementary and alternative medicine (CAM) is the most ancient therapeutic practice in the world, which remains very common in Africa [8]. CAM has evolved, to give rise to modern therapy, whereby manufactured drugs are produced as a result of stringent research protocols, which enables substantial reduction of side/toxic effects. However, original CAM, basically consisting of the use of original materials in the natural way, is still commonly practiced nowadays by populations of both industrialized and developing countries. This practice is even increasing among all populations, probably motivated by the beliefs from populations, who consider medicinal plants (*i.e.*, plants that have at least one of their chemical components and/or structural parts—flowers, leaves, stem, seeds, barks, or roots—used for therapeutic purposes [9] as natural and

therefore less "harmful" than manufactured/synthesized drugs used in conventional medicine. In fact, the use of synthetic drugs in order to relieve or treat multiple diseases has been associated with many side effects and undesirable hazards. People have thus gone back to CAM, and particularly to extracts from medicinal plants, which are culturally acceptable, easily available, and economically viable [10]. Indeed, in rural areas of developing countries, the medicinal plants continue to be used as the primary source of medicine. About 80% of the people in developing countries use traditional medicines for their healthcare [11]. An impressive number of medicinal plants are currently used worldwide against diseases, and hepatoprotective and hepatocurative medicinal plant preparations have unique importance. In fact, liver diseases are among the most serious health challenges ravaging the world now. Liver diseases may be classified as acute or chronic hepatitis (inflammatory liver diseases), hepatosis (non-inflammatory diseases), and cirrhosis (degenerative disorder resulting in fibrosis of the liver) [10] [12]. Although liver metabolic process is aimed at converting xenobiotics into water-soluble metabolites in order to facilitate further elimination in the urine, it may also lead to bioactivation of the xenobiotics into highly hepatotoxic compounds. The prevention and treatment options for liver diseases remain scarce nowadays despite tremendous advances in modern medicine [10] [13]. Except for vaccines and interferon α-2b, which concern only viral infections, modern medicine is quite limited in treating liver diseases, and only a few available drugs include cholagogues, choleretics, drugs for cholesterolic lithiasis, N-acetylcysteine (NAC), alkaloid mixture from *Enantia chlorantha* (Hepazor), and flavolignans from *Silybum marianum* [14] [15]. This encourages frequent use of medicinal plants as hepatoprotective or hepatocurative. Several reports and reviews do exist on modulation of liver function by medicinal plants from Asia, Europe, and America. However, protection of the liver by medicinal plants from Africa is still scanty, and the few available ones remain scattered. This research focuses on hepatoprotective medicinal plants that are used in folkloric medicine in Africa.

Erythrina senegalensis (**Figure 1**) is commonly found in Mali, Senegal and Nigeria. It is mainly grown in West Africa as an ornamental plant [16]. *Erythrina senegalensis* DC (Fabaceae) is a thorny shrub or small tree with common names that include coral tree (English) and minjirya (Hausa, Nigeria). The stem and root bark are used by traditional healers to cure wide range of illnesses [17] [18] [19]. The leaves are used to treat malaria, gastrointestinal disorders, fever, dizziness, secondary sterility, diarrhea, jaundice, nose bleeding and relieve pain [18]. The stem barks have been shown to possess antimicrobial activities [20] and also inhibits HIV-1 protease [21]. The hepatoprotective activities of the stem bark have also been documented [22]. The bark and root decoction is used for stomach disorder and hepatoprotective properties [16]. In Cameroon and Nigeria, decoctions made from different parts of the plant are taken orally or in body baths to treat malaria, fever, cough, snake bites, inflammation and prostate [18].

Figure 1. *Erythrina senegalensis*.

In Cameroon also, the stem bark is used to treat liver disorders [23]. Prynylflavonoids; 8-prenylleutone; auriculatin; erysengalensin O, D and N; derrone; alpinumisoflavone and 6, 8-diprenylgenisten have all been isolated from *E. senegalensis* and have demonstrated antimicrobial and pharmacological activities [24]. As the liver is actively involved in a variety of drug metabolism, protection of the liver from the deleterious effects of drug metabolites is of utmost importance. The leaf of *E. senegalensis* is very popular in inflammation management in South Eastern Nigeria because it offers inexpensive, readily available and effective approach to treatment of wounds and inflammation, yet scientific validation of this pharmacological activity has not been done. This study evaluates the hepatoprotective activity of aqueous extract of *E. senegalensis* on paracetamol induced liver damage in wistar albino rats.

2. Materials and Methods

2.1. Collection of Plant Material

The stem cuttings of *Erythrina senegalensis* were collected from the Plateau State University, Bokkos, environment. The collected samples were washed thoroughly in running tap water and were dried in a shade away from direct sunshine. The dried samples were crushed using mortar and pestle. The fine powder was obtained by sieving. After weighing, the powder was packed in clean labelled bottles and stored until use.

2.2. Preparation of Aqueous Extract

Extraction was performed by macerating air-dried, powdered stem cuttings of *Erythrina senegalensis* (60 g) soaked in distilled water (600 ml) at room temperature for 72 hrs and was occasionally shaken. The crude aqueous extract was filtered using Whatman No. 1 filter paper and was concentrated in a water bath at 70˚C to obtain concentrated extract and was allowed to air dry in a beaker. The dry residue was stored at 4˚C, and at the time of use, was re-suspended in dis-

tilled water.

2.3. Preparation of Ethanolic Extract

Extraction was performed by macerating air-dried, powdered *E. senegalensis* (60 g) soaked in 10% ethanol (600 ml) at room temperature for 24 hrs and was occasionally shaken. The crude 10% ethanolic extract was filtered using, Whatman NO. 1 filter paper, concentrated using a water bath at 78˚C to remove the ethanol and to obtain concentrated extract and was allowed to air dry in a beaker. The dry residue was stored at 4˚C, and at the time of use, was re-suspended in distilled water.

2.4. Preparation of Stock Plant Extract Solutions

Preparation of the solution was done by dissolving four (4.00) grams of the powdered extract in ten millilitres of distilled water to give a solution of concentration 400 mg/ml of *Erythrina senegalensis* aqueous extracts. The stock solution was prepared for administering to the rats. The volumes of the extract administered to the animals were calculated using the formula by Gosh (1984) as shown below:

$$\text{Volume given to each animal}(\text{mL}) = \frac{\text{body weight of animals}(\text{kg}) \times \text{dose}(\text{mg/kg})}{\text{concentration of extract}(\text{mg/mL})}$$

2.5. Experimental Animals

Wistar rats weighing between 100 to 380 g were purchased from the small animal facility of the National Veterinary Research Institute (NVRI) Vom. The animals were kept in metal cages in a well-ventilated room and allowed to acclimatize for 14 days. The animals were fed with standard pelleted rat feed from Dagwom farm mill, NVRI Vom, with drinking water provided ad libitum. All experiments were conducted in accordance with the principles and guidelines for the care and use of laboratory animals. (NRC, 1996) and approved by the animals' welfare and ethics committee of the NVRI Vom.

2.6. Experimental Design

A total of 18 rats were used. The rats were randomly divided, into six groups of three rats each and treated orally as follows for 4 days, 72hrs after the induction of liver damage:

Group A: Negative control, received normal saline orally.

Group B: Positive control, administered with paracetamol 1500 mg/kg body wt. in distilled water.

Group C: Paracetamol as in group B + 200 mg/kg b. wt. of the aqueous root extract of *Erythrina senegalensis*.

Group D: Paracetamol as in group B + 300 mg/kg b. wt. of the aqueous root extract of *Erythrina senegalensis*.

Group E: Paracetamol as in group B + 400 mg/kg b. wt. of the root extract of

Erythrina senegalensis.

Group F: Paracetamol as in group B + 500 mg/kg b. wt. of the root extract of *Erythrina senegalensis*.

On the sixth day, all the animals were sacrificed under chloroform anaesthesia and blood samples were collected.

2.7. Biochemical Analysis

The blood collected was allowed to clot for 30 minutes and centrifuged at 3000 rpm (revolution per minute) for 5 minutes to obtain serum. The supernatant was collected using Pasteur pipette into sample bottles. The serum was used for biochemical estimations of some liver enzymes; alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). The activities of serum transaminases (ALT and AST), were assayed using the methods of Reitman and Frankel [25] Reitman & Frankel, 1957). Serum alkaline phosphatase activity was determined using the method of King and Armstrong.

2.8. Rats Bleeding

The rats were bled by puncture of the median canthus of the eye using a capillary tube and the blood was collected in a plain tube. Two to three millilitres of the blood sample were centrifuged at 3000 rmp for 30 mins. The serum was separated from the blood and kept in a clean tube and stored in a refrigerator for the liver function test.

2.9. Statistical Analysis

Data for this study were analyzed using SAS version 9.4 and figures were created using Graph pad prism 8 and Microsoft Excel version 20. Results are expressed as mean ± standard deviation. Statistically significant differences are recorded at $p < 0.05$ at 95 confidence interval (CI). One way analyses of variance with tukey post hoc analysis was used to compare the means values within groups.

3. Results

Biochemical Parameters

The hepatic enzymes (AST, ALT, and ALP) in serum significantly ($p < 0.05$) increased in positive PCM-control group (75.33 ± 2.88 U/L, 57.9.53 ± 9.54 U/L and 321.41 ± 1.23 U/L) as shown In **Figures 2-4** respectively when compared to the negative control group (35.67 ± 2.88 U/L, 56.00 ± 19.37 U/L and 222.39 ± 3.19 U/L) and respectively. The aqueous extract of *Erythrina senegalensis* stem treatment with (300 mg/kg) showed decreased ALT and ALP levels (37.30 ± 2.86 and 236.00 ± 5.78 U/L) respectively, while AST level was slightly decreased (57.33 ± 9.50 U/L) when compared to paracetamol-control group (AST = 57.53 ± 9.54) as showed in **Figure 3**. The aqueous stem extract of *Erythrina senegalensis* stem treatment with (200 mg/kg) and (400 mg/kg) (44.64 ± 6.64 U/L, 40.33 ± 2.30 U/L and 43.8 ± 14.56 U/L) and (54.00 ± 5.19 U/L, 43.30 ± 4.54 U/L and

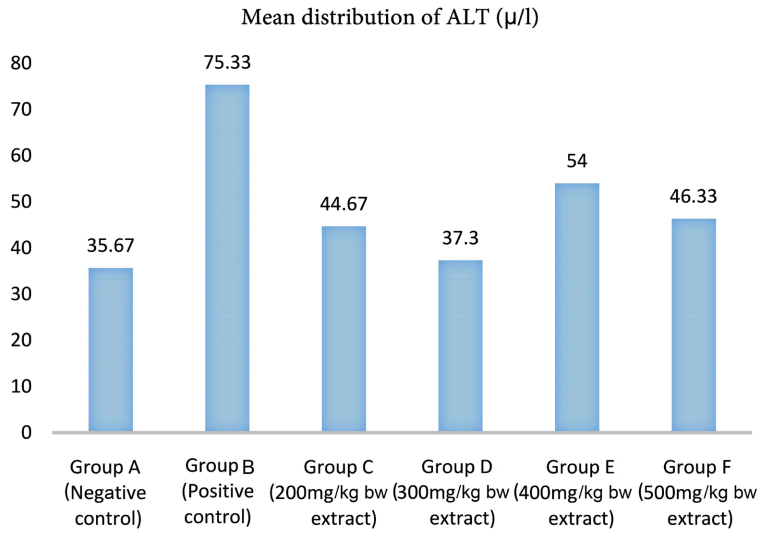

Figure 2. Mean Distribution of ALT (U/L) within Experimental Animal Groups.

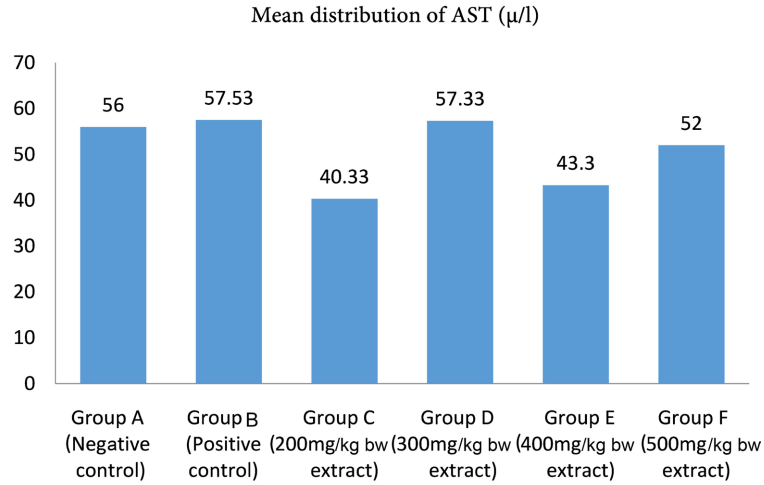

Figure 3. Mean Distribution of AST (U/L) within Experimental Animal Groups.

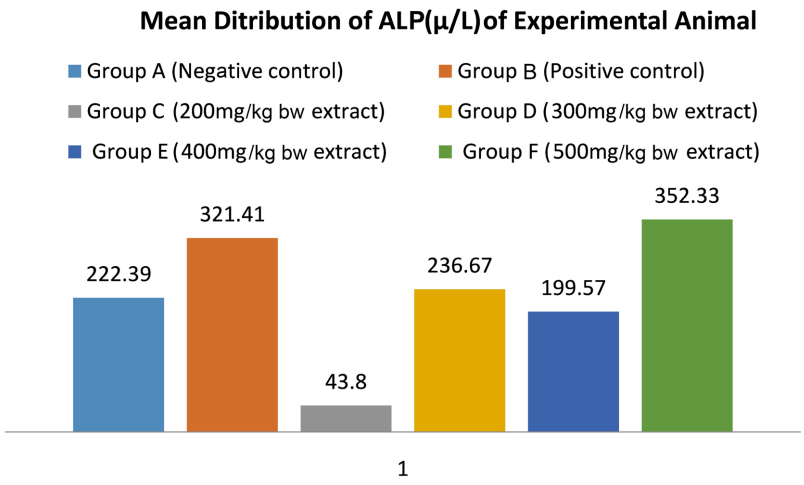

Figure 4. Mean Distribution of ALP (U/L) within Experimental Animal Groups.

199.57 ± 2.14 U/L) has showed decreased in serum level of AST, ALT and ALP, respectively when compared to paracetamol-treated animals. However, the group treated with, (500 mg/kg) of the aqueous extract, showed decrease in the levels of ALT and AST (46.33 ± 11.59 U/L and 52.00 ± 10.00 U/L) respectively as compared with the (PCM-control) except in the levels of ALP which was increased significantly (from 321.41 ± 1.23 U/L to 352.33 ± 47.77 U/L) as shown in **Figure 4**.

Data expressed as Mean ± Standard Deviation (SD) of triplicate readings, significant mean difference at 95 confidence interval (CI) is $p < 0.05$.

4. Discussion

Medicinal plant-based medicines are potential sources of naturally occurring phytoconstituents that may act in a variety of ways to suppress the generation of reactive oxygen species. These phytoconstituents have broad ranges of pharmacological activities [26]. Glutathione is one of the major antioxidants that protect the liver from toxic effects of paracetamol [27], but overdoses of paracetamol may result in the depletion of glutathione stores, which ultimately leads to the release of serum levels of liver enzyme biomarkers indicating mitochondrial damage [28]. Paracetamol (PCM) is a common antipyretic agent that is safe in therapeutic doses but can produce fatal hepatic necrosis in man and experimental animals with toxic doses [29].

Paracetamol is metabolized primarily in the liver and eliminated by conjugation with sulfate and glucuronide, thereafter it is then excreted by the kidney. Nevertheless, paracetamol hepatotoxicity has been linked to the formation of toxic metabolites, when a part of it is activated by hepatic cytochrome P-450 to a highly reactive metabolite N-acetylp-benzoquinoneimine (NAPQI). Toxic metabolites (N-acetylp-benzoquineimine) can alkylate and oxidize intracellular GSH, which results in liver GSH depletion subsequently leading to increased lipid peroxidation by abstracting hydrogen from a polyunsaturated fatty acid and ultimately, liver damage caused by higher doses of paracetamol. Due to liver damage, cellular leakage and loss of functional integrity result in elevated serum enzyme levels [30].

The greatest amount of alanine transaminase (ALT) and aspartate transaminase (AST) are found in the liver followed by a lesser amount in the heart and in the skeletal muscles. When cells in these tissues are injured, these enzymes are released into the blood resulting in their elevated serum levels. Since the liver contains the highest levels of both transaminases, any damage to the cells of the liver would result in elevated levels of (ALT and AST) in the serum. The degree of elevation is usually linked to the severity of the hepatocellular damage [31], hence assessment of liver function can be carried out by quantifying these enzymes in the serum.

In the present study, paracetamol-induced acute hepatic damage as evidenced by a marked elevation in the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) as compared with the

control group. The altered levels of these enzymes are in agreement with the degree of liver damage induced by paracetamol. The increase in the levels of transaminases and alkaline phosphatase is a clear indication of cellular leakage and loss of functional integrity of the membrane resulting from liver injury [32]. Treatment with the aqueous extract of *Erythrina senegalensis* stem altered the levels of these marker enzymes to near normal or only slightly elevated as compared with the control group, indicating a dose-dependent protection against liver damage. Treatments with 200 mg/kg, 300 mg/kg and 400 mg/kg b.w of the aqueous extract showed a decrease in the liver enzymes levels that may be attributed to high concentration of phytonutrients like the flavonoids which have antioxidant properties that will help boost its protective effect. At 500 mg/kg of the aqueous extract of *Erythrina senegalensis* an increase in the level of ALP liver enzymes levels was observed, this might be due to the fact that high concentration of the extracts can cause the elevation in the level of the alkaline phosphatase. Since 500 mg/kg body weight was the highest dose of the *Erythrina senegalensis* extract given, high concentration of the extracts may be the reason behind the elevated levels of the liver enzymes. What that could be inferred from above is that the practice of high dosage of the extracts ingestion may not give the desired hepato-protective result.

However, treatment with 200 mg/kg of the aqueous extract and 400 mg/kg of the aqueous extract of *Erythrina senegalensis* was found to significantly restore the PCM-induced alterations closer to normalcy by decreasing the levels of AST and ALT and ALP except in ALP. Hence, a reduction in the levels of these transaminases demonstrates membrane stabilizing activity of the extract and regeneration process of hepatocytes. This is in agreement with the commonly accepted view that serum levels of AST, ALT, and ALP return to normal with the healing of hepatic parenchyma and the regeneration of hepatocytes. The significant reduction in liver enzymes after treatment, suggests that the extract possesses hepatoprotective property [31].

In the muscle, ALT catalyzes the conversion of alanine to pyruvate and glutamate and is released in similar manner. Therefore, AST is more specific to liver and thus a better parameter for detecting liver damage [32]. In addition to that, high levels of ALT in the serum has been shown to be as a result of hepatocellular damage indicative of the fact that PCM has damaging effect on liver tissues.

The alterations in the levels of ALT and AST in the treated groups possibly occur due to the presence of flavonoids in the extracts used. Various phytoconstituents such as alkaloids, flavonoids and other phenolic constituents present in the plant extract could be responsible for the membrane-stabilizing activity. Elevated levels of these enzymes in the serum represent the loss of functional integrity due to the cellular leakage of these enzymes from the cell membrane of the liver [33]. Estimations of these liver enzyme markers in the serum reflect the normal and/or abnormal condition of the liver. A high dose of *Erythrina senegalensis* showed a nonsignificant difference with the hepatoprotective effects of standard drug of acetaminophen. Various phytoconstituents such as alkaloids,

flavonoids and other phenolic constituents present in the plant extract could be responsible for the membrane-stabilizing activity.

5. Conclusions

Based on this study, it can be deduced that the hepatoprotective property of the stem extract of *Erythrina senegalensis* is dose-dependent and also dependent on the method used for the extract. The results of the present study reveal that the aqueous extract of *Erythrina senegalensis* can significantly protect the liver from the damaging effects of paracetamol in a dose-dependent manner by considerably decreasing the serum levels of liver enzyme markers. At 200 mg/kg, 300 mg/kg of the aqueous extract and 400 mg/kg of the ethanolic extract of the aqueous extracts of *Erythrina senegalensis* has hepatoprotective action on PCM-induced hepatotoxicity in rats, which may be attributed to the presence of phytoconstituents, such as alkaloids, flavonoids, glycosides, and other phytochemicals in the plant extract.

However, the mechanism of hepatoprotection seems to involve the modulation of the antioxidant enzyme systems but at 500 mg/kg has shown decreased in ALT and AST but a slight increase in elevated level of ALP. These beneficial effects may be attributed to the individual or combined action of the phytoconstituents present in the extract. Therefore, it is pertinent to further determine, isolate and purify the extract's bioactive constituents with the potential hepatoprotective property and also to identify both the exact mechanism(s) of action and active phytoconstituent(s) involved in this effect for future studies. Studies can also be carried out to check the effect of the plant extract on other tissues of the body like the heart and spleen. The hepatoprotective effects of *Erythrina senegalensis* scientifically validate the traditional use of *Erythrina senegalensis* in liver ailments.

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Conflicts of Interest

The authors declare no conflict of interest with regards to the publication of this paper.

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