REGULATED EFFECTS OF *CAPSICUM FRUTESCENS* SUPPLEMENTED DIET (C.F.S.D) ON FASTING BLOOD GLUCOSE LEVEL AND BIOCHEMICAL PARAMETERS IN ALLOXAN INDUCED DIABETIC WISTAR RATS.

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ABSTRACT

Aim of the study: Assessment of the effects of *Capsicum frutescens* supplemented diet (C.F.S.D) on fasting blood glucose level and biochemical parameters in alloxan induced diabetic Wistar rats.

Experimental Design: 130 – 150g healthy forty male Wistar rats were divided into four groups as following~~:~~ : Group 1 served as a normal control and received normal feed~~.~~ , Group 2 (Diabetic control) received normal feed~~.~~, Group 3 (Diabetic test 1) received normal feed + 1g Capsicum frutescens~~.~~ , Group 4 (Diabetic test 2) received normal feed + 2g Capsicum frutescens.

Place and Duration of study: This study was carried out in the department of Physiology, Faculty of Basic Medical Sciences, Delta State University, Abraka and the feeding lasted for three weeks. At the end of the experiments, ~~the animals were sacrificed,~~ blood samples were collected and then the serum was further subjected to biochemical analysis using biochemical analyzer (Reflotron Plus).

Results: AST, ALT, ALP, GGT, Creatinine, Uric acid, total cholesterol and fasting blood sugar level in serum were increased, however the high density lipoprotein cholesterol (HDL-c) ~~of~~ in serum was decreased in diabetic control (group 2), compared with ~~non-diabetic control~~normal control (group 1). The administered *Capsicum frutescens* in the diet ~~at 1g and 2g doses~~ significantly reduced the fasting blood glucose level as well as the serum level of AST, ALT, ALP, GGT, Creatinine, Uric acid, total cholesterol, compared with diabetic control. Serum HDL was also significantly increased in Capsicum frutescens group~~swhen~~ compared with diabetic control P<0.05, and ~~. Decrease in body weight in diabetic control group and increased~~ increasing ~~in~~ body weight ~~of 1gand 2g Capsicum frutescens supplemented diet groups~~ were also observed as well.

Conclusion: ~~The observed improvement in the biochemical parameters and body weight of alloxan induced diabetic Wistar rats by 1g and 2g~~ *Capsicum frutescens* supplemented diet

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can ameliorate ~~–~~alloxan induced diabetic Wistar ratssuggests ~~*Capsicum frutescens* to possess, cardio-protective and anti-diabetic properties~~.

Recommendation: ~~The incorporation of~~ *Capsicum frutescens*, as spice in the diet, is benefits for the ~~of individuals who are~~ diabetic patients~~, hypertensive and obese, is worthy of recommendation~~.

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Keywords: Capsicum Frutescens, Fasting Blood Glucose, Liver enzymes, Capsaicin, Thermogenesis.

1. INTRODUCTION

Diabetes mellitus (DM) has been described as a multifactorial disease that is characterized by hyperglycemia and lipoprotein disorders [1], increased basal metabolic rate [2], defect in reactive oxygen species scavenging enzymes, as well as altered intermediary metabolism of major food substances [2]. Diabetes is a major degenerative disease in the world today [3], affecting at least 15 million people and having complications which include hypertension, atherosclerosis and microcirculatory disorders. Diabetes mellitus is a syndrome of impaired carbohydrate, fat and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissue to insulin.

At least 80% of Africans rely on plant medicine for their healthcare [4]. Today, medicinal plants are increasingly being used in most parts of the world as: hypolipidemic [5]; antihypertensive [6]; treatment for skin diseases [7] and hypoglycemic [8].

For the past 25 years, epidemiological studies have revealed a diminished risk of chronic diseases in populations consuming diets fortified with fruits and vegetables, [9]. ~~It has been suggested that antioxidants found in large quantities in fruits and vegetables may be responsible for this protective effect, [10].~~ In the past three decades, it has been experimentally documented that several common spices can ~~also~~ exert health beneficial physiological effects, [11; 12]. These physiological effects of spices in most instances have been traced to the bioactive chemicals (Among these physiological effects of spices documented are hypolipidemic and antioxidant properties with beneficial health implications, [13]).

One of such phytomedicine is *Capsicum frutescens*, a short lived evergreen shrub that usually grows from 1 to 1.5m in height and 1 to 3cm in basal stem diameter. It is commonly recognized by its fruit, the large red, orange, or yellow chili peppers that the plant produces.

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Capsicum frutescens fruits grow as long pods, and when ripe they develop their characteristic warm coloring. Its species likely originated in south or Central America. It spread quickly throughout the subtropical regions in the area and still grows wild today. The plant grows in tropical climates, because it needs a warm, humid climate to survive. It had been reportedly used in the treatment of various ailments such as diabetes, blood pressure [high/ low], bronchitis, burning feet, arthritis, etc [14].

Accumulating evidence has shown multiple pharmacological effects of Capsicum on a variety of physiological systems such as cardiovascular system, gastro-intestinal tract, metabolic rate, and pain relief, [15].

Previous research had shown the ~~Chemo~~chemo-~~Protective~~ protective effect of spices among which are including:~~;~~ *Turmeric*, *Capsicum frutescens*, *Cloves*, and *Cardamom* on ~~Correcting~~ correcting ~~Iron~~ iron ~~Overload~~overload-~~Induced~~ induced ~~Liver~~ liver ~~Injury~~injury, ~~Oxidative~~ oxidative ~~Stress~~ stress and ~~Serum~~ serum ~~Lipid~~ lipid ~~Profile~~ profile in ~~Rat~~ rat ~~Model~~model. The incorporation of chili (*Capsicum frutescens*) in the diet at 2 % significantly restored the enzyme activities of the liver AST, ALT, and ALP to normal level. The mean values of lipid profile, the MDA and serum total bilirubin were also reduced~~,~~ [16].

The bioactive ~~ingredience~~ ingredients in *Capsicum frutescens* ~~that~~ gives the hot and spicy flavor that was identified as capsaicin, [15]. Red chili (RC) (*Capsicum frutescens)* is widely used as a spice for flavoring foods, particularly in South- East Asian and Latin-American countries. Several studies indicate capsaicin (red pepper) is an appetite suppressant which can slightly increase metabolism. Spicing up one's foods with capsaicin-containing spices and using red pepper as a condiment can aid in increasing the rate of fat burning or thermogenesis. ~~In an article published in the British Journal of Nutrition,~~ Yoshioka et al (2001)[17] concluded that the consumption of red pepper and caffeine can induce a considerable change in energy balance when individuals are given free access to foods. Pungent capsaicinoids (capsaicin, dihydrocapsaincin), antioxidant vitamins (ascorbic acid, vitamin E), carotenoids (β-carotene, β- cryptoxanthine) and several organic acids and minerals are the major active ingredients of *Capsicum frutescens,* [18]. Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) is an irritant for mammals, including humans, and produces a sensation of burning in any tissue ~~with which it comes into contact~~. Capsaicin and several related compounds are called capsaicinoids and are produced as a secondary metabolite probably as deterrents against certain herbivores and fungi. The burning and painful sensations associated with capsaicin result from its chemical interaction with sensory neurons. Capsaicin, as a member of the vanilloid family, binds to a receptor called the vanilloid receptor subtype 1 (VR1), [19].

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Diabetes mellitus ~~that arise~~ results from ~~as a result of~~ insulin insufficiency which is associated with altered activity of various biochemical parameters such as alkaline phosphatase (ALP), alanine transaminase (ALT), aspertate transaminase (AST), serum electrolyte, lipid profile, among other biochemical parameters, [20; 21].

Because the liver plays a critical role in the maintenance of carbohydrate homeostasis, it is not surprising that its functions may be affected in a hyperglemic state as the normal metabolic functions of the liver are over stretched.

However, there are not enough scientific information on the effects of *Capsicum frutescens* supplemented diet on biochemical parameters of alloxan induced diabetes in Wistar rats. The present study was designed depending on this background.

2. MATERIAL AND METHODS

Chemicals and equipments:

All chemical used in the research were procured as follows:

Red Chili (*Capsicum frutescens*), purchased from Abraka market in Ethiope East local government area, Delta State, which was authenticated by Dr. (Mrs). N.E. Edema in the department of Botany, Faculty of Science, Delta State University, Abraka. It was then air-dried at room temperature (22±1^{o}C) for 14 days until a constant weight was attained and was then blended with the aid of a grinding machine and stored in an airtight container for use in the experiment. Alloxan monohydrate (Sigma, alpha Aesar, 25g. A15324, CAS:2244-11-3. Cotton wool, Hand gloves, Dissecting kit, Centrifuge, Pipettes, Growers mash ,Beakers, Electronic weighing balance, Syringes and needles, Marker pen, Oncall Redii Glucometer and Reflorton plus$^{(R)}$ reflectance photometer (Roch Diagnostic GmbH, D-68298).

FRESH AND DRIED *CAPISCUM FRUTESCENS FRUITS*

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~~FRESH AND DRIED *CAPISCUM FRUTESCENS FRUITS*~~

PREPARATION OF PEPPER SUPLEMENTED DIET

1g and 2g *Capsicum frutescence* supplemented diet were prepared as following: weighing 1g and 2g of powdered Capsicum frutescence and mixing them with 99g and 98g of animal feed (growers mash), respectively.

COMPOSITION OF THE GROWERS MARSH

Protein-19.0%

Fat -2.85%

Fibre – 6.00%

Calcium – 1.00%

Available phosphate – 0.45%

Energy – 2875 KGC

(Animal Care Services Konsult (NIG) LTD).

HANDLING OF EXPERIMENTAL ANIMALS

Forty (40) healthy Male Wistar rats weighing 130-150g were from the International institute of tropical agriculture, (IITA), Ibadan Nigeria. They were acclimatized for 14-days at in the animal house unit in the Department of Pharmacology, Faculty of Basic Medical Science, Delta State University Abraka before the experiment. The rats were kept in well ventilated wooden cages. They were exposed to 12 hours of natural daylight and darkness and fed standard rat feed and water *ad libitum*. Procedures ~~followed in~~ of raising the experimental animals were in accordance with the ethical standards of the Institutional Animals Ethics Committee (IAEC). And permission for the use of animals and animal protocol was obtained from the Research Ethics Committee of Delta State University, Abraka.

Induction of diabetes

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Thirty (30) animals were fasted for 24hours (but with free access to water) and then the diabetic model was reproduced by injecting a single intraperitonial dose of alloxan monohydrate (150mg/kg) which prepared in stock of 1500mg/50ml and a concentration of 30mg/ml. After three days, rats with fasting blood glucose concentration ~~above~~ over 200mg/dl were confirmed diabetic. Diabetic state was maintained for three days for well establishment of diabetes.

Comment [L1]: Only three day?

EXPERIMENTAL PROCEDURE

Diabetes mellitus rats were randomly allotted into 3 different groups and non diabetic rats as normal control (Group 1) as following~~:~~:

Group 1: Non diabetic rats received normal diet (non-diabetic control)

Group 2: Diabetic rats received normal diet (diabetic control)

Group 3: Diabetic rats received 1g *Capsicum frutescens* supplemented diet (test 1 group)

Group 4: diabetic rats received 2g *Capsicum frutescens* supplemented diet (test 2 group).

Each animal was fed a 5g meal formulated by mixing 1g and 2g *Capsicum frutescens* with 99g and 98g animal feed and treatment was ~~done~~ twice daily for ~~twenty one~~21 days. Rats' initial body weight prior to commencement of treatment was recorded. ~~Inclusion criteria in this study were; non diabetic that were not induced with diabetes (which served as positive control), and animals with evidence of diabetes. Exclusion criteria include those animals that died during the maintenance of diabetes. Thus higher numbers of animals were allocated to groups 1, 2 and 3.~~

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BLOOD COLLECTION AND BIOCHEMICAL ASSAY

After ~~twenty one~~21 days ~~of~~ treatment, all overnight fasted rats were anaesthetized using chloroform and then sacrificed. Blood samples collected by cardiac puncture were delivered into lithium heparin bottles. The tubes were then centrifuged at 4000 rpm for ten minutes to obtain ~~clear~~ serum which were ~~later subjected to~~ used for biochemical evaluation for ALT, AST, ALP, GGT, URIC ACID, CREATININE, HDL, and TOTAL CHOLESTEROL using Reflotron plus kit.

Fasting blood glucose level was determined with ~~the aid of~~ glucose analyzer machine (Oncall- Redii glucometer) by collecting blood samples from tail veins of overnight fasted animals. Values were expressed in mg/dl.

STATISTICAL ANALYSIS

The result ~~of this study were~~ was expressed as mean ± SEM, and were analyzed by one way analyses of variance (ANOVA) using statistical package for social science (SPSS, 16). Difference between the means were tested with post Hoc- Tukey's test for multiple comparison and significance was considered when $p< 0.05$. Student's dependent t-test was

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used to analyze the significant difference between body weight before treatment and after treatment.

3. RESULTS AND DISCUSSION

Table 1:

Effects of *Capsicum frutescens* supplemented diet on biochemical parameters of alloxan induced diabetic Wistar.

	Group 1: Non-Diabetic control	Group 2: Diabetic control	Group 3: Diabetic +1g C.F.S.D	Group 4: Diabetic + 2g C.F.S.D.
Creatinine (IU/L)	0.42 ± 0.03	0.94 ± 0.17[a]	0.4 ± 0.3[b]	0.54 ± 0.07[b]
Uric acid (IU/L)	5.49 ± 0.2	7.87 ± 0.85[a]	5.03 ± 0.2[b]	6.3 ± 0.7
GGT (IU/L)	223.4 ± 7.5	275.0 ± 10.7[a]	221.8 ± 6.4[b]	224.8 ± 6.0[b]
AST (IU/L)	278.4 ± 19.6	325.2 ± 26.1	247.2 ± 10.8[b]	251.8 ± 12.3
ALP (IU/L)	251 ± 6.81*	316.4 ± 37.7*	327.6 ± 27.6*	243.8 ± 4.53*
ALT (IU/L)	61.7 ± 1.03*	128.2 ± 32.97*	98.98 ± 8.74*	87.86 ± 8.54*
HDL (mg/dl)	47.98 ± 1.8[ns]	43.1 ± 2.8	46.8 ± 1.6[ns]	46.0 ± 1.4[ns]
T.Cholesterol (mg/dl)	85.6 ± 5.6	79.2 ± 4.4	101.6 ± 3.3[b]	61.5 ± 3.4[abc]
InitialBlood glucoselevel (mg/dl)	88.8 ± 6.22	380.2 ± 16.6	363.8 ± 24.3[d]	382.2 ± 14.7[d]
FinalBlood glucoselevel (mg/dl)	94.8 ± 6.18 (6.8%)	370.0 ± 19.81[a] (-2.63%)	182.8 ± 16.82[abd] (-49.8%)	146.6 ± 14.8[bd] (-61.6%)

Values are expressed as mean ± Standard error of mean (S.E.M), n=10 *P<0.05: Significant as determined by one way analysis of variance. Significant difference ([abc]P < 0.05): (a) compared to group 1, (b): to group 2, (c): to group 3.[d]P<0.05: Significant when initial and final fasting blood glucose level were compared in groups 3 and 4. Values in parenthesis depict the percentage change in FBGL when initial and final values were compared. Significant difference ([ns]P< 0.05) HDL, comparing groups 1, 3, 4 with group 2 .

AST- (Aspartate Transaminase)

ALT- (Alanine amino Transaminase)

ALP- (Alkaline Phosphatase)

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GGT- (Gamma Glutamyl Transpeptidase)

They are all liver enzymes(biomarkers) of liver damage.

Table 2:

Effects of Capsicum frutescens (C.F.) supplemented diet on body weight of alloxan induced diabetic rats.

	Body weight before treatment Week 0 (g)	**Body weight after treatment Week 3 (g)**
Group 1 (Normal control)	131 ± 9.8	195 ± 17.2 (48.9%)
Group 2 (Diabetic control)	140 ± 9.6	120 ± 7.9 (-16.7%)
Group 3 (Diabetic, 1g C.F.S.D)	125 ± 6.7	134 ± 19.2 (7.2%)
Group 4 (Diabetic, 2g C.F.S.D)	140 ± 7.2	152 ± 16.9 (8.5%)

Values are expressed as mean ± Standard error of mean (SEM), n = five animals per group. C.F: Capsicum frutescence.

~~DISCUSSION~~

The action of capsaicin is mediated by TPRV1 (vanilloid receptor), which belongs to an ion channel group. VR1 when activated permits cations to pass through the cell membrane and into the cell resulting in depolarization of the neuron stimulating it to signal the brain. By binding to the VR1 receptor, the capsaicin molecule produces the same sensation that excessive heat or abrasive damage ~~would cause~~, explaining why the spiciness of capsaicin is described as a burning sensation. The inflammation resulting from exposure to Capsaicin is believed to be the result of the body's reaction to nerve excitement rather than just chemical burn or any direct tissue damage when chili peppers are the source of exposure. Capsaicin is the chemical compound in chili peppers that contributes to their spiciness~~;~~. ~~capsaicin~~ Capsaicin stimulates a receptor found in sensory neurons, creating the heat sensation and subsequent reactions like redness and sweating.

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In the study by Yoshioka et al (2001)[17], 8.6g and 7.2g red pepper were added to lunch and dinner respectively. Red pepper and caffeine consumption significantly reduced the cumulative ad libitum energy intake and increased energy expenditure. Almost 1000 additional calories per day were burned by combining caffeine consumption with substances containing red pepper.

~~The New York Daily News published an article "15 fat-burning foods" about the capsaicin and caffeine combination that simply states "men who consume coffee and red pepper-packed snacks and meal burned almost 1000 more calories a day then the control group".~~

Yasser (2008)[22] found that capsaicin can create "heat" in a more direct manner by altering the activity of a muscle protein called SERCA. Normally, muscle contraction is initiated following the release of a wave of calcium ions from a compartment called the sarcoplasmic reticulum. SERCA then actively pumps the calcium back into the sarcoplasmic reticulum (using ATP energy), causing muscle relaxation and renewing the cycle. Capsaicin, however can attach to SERCA and "uncouple" this pumping activity, that is, the protein still burns ATP energy but does not use it to pump calcium. Instead, all the ATP energy is given off as heat. This uncoupling known as thermogenesis, is one important method of staying warm and is most often seen in hibernating animals. Yasser noted also that capsaicin is the first natural compound known to augment the thermogenesis process. The findings further explained how capsaicin intake can increase metabolism and body temperature. The study also noted that though relatively high amounts of capsaicin (probably more than someone could eat), was required to effectively achieve the desired result, but the structure of capsaicin could be used as a model of design more potent compounds that might have clinical use such as treating hypothermia.

Avraham et al (2008)[23] in their study tittled " Cannabinoids and capsaicin improve liver function following thioacetamide-induced acute injury in mice", reported an improvement both in liver pathology and function.

Results of the present study, showed decrease in body weight from (140 ± 9.6), before treatment to (120 ± 7.9), after treatment [Table 2]. Body weight of 1g and 2g *Capsicum frutescens* supplemented diet treated groups were increased ~~more than rats in~~compared with group 2. This could be traced to the recovery effects of *Capsicum frutescens* against weight loss associated with diabetes mellitus caused by alloxan monohydrate.

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Comment [L4]: Please consider this sentence.

Comment [L5]: From the before discussion, capsaicin can expense energy, how did it increase the body weight?

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Significant reduction in FBGL in 1g (group 3) and 2g (group 4) C.F.S.D treated groups may be attributed to the presence of hypoglycemic agents in *Capsicum frutescens*. Studies had shown that *Capsicum frutescens* is used to treat diabetes mellitus by traditional healers in Jamaica, [24]. Pharmacokinetic and the effect of Capsaicin in *Capsicum Frutescens* on decreasing ~~Plasma Glucose Level~~ blood glucose level in a crossover study of 12 healthy volunteers by performing the OGTT while receiving placebo or 5 grams of capsicum had been documented [25].

Impaired carbohydrate utilization in the diabetic also leads to accelerated lipolysis, which results in elevated plasma triglycerides levels (hyperlipidemia), [26]. The observed abnormalities of triglyceride and HDL metabolism are in accordance with reports on early manifestation of insulin resistance, the precursor to diabetes [27; 28]. From the result of the study, 2g C.F.S.D treated group elicited reduction in serum level of total cholesterol than 1% treated group. The physiological effects of most spices had been documented to exhibit hypolipidemic and antioxidant properties with beneficial health implication, [13].

Individuals with type 2 diabetes had also been reported to have a higher incidence of liver function test abnormalities than non diabetic individuals. Mild chronic elevations of transaminases often reflect underlying insulin resistance. Diabetes mellitus can arise as a result of insulin insufficiency, which is associated with altered activity of various liver enzymes, [20]. Grossi, *et al*., (1998)[21] had also reported that values of serum ALP can be raised in diabetic patients. The liver releases alanine aminotransferase (ALT) and an elevation in plasma concentrations are an indicator of liver damage, [28]**.** The levels of aspertate aminotransferase (AST), alanine amino transaminase (ALT) and alkaline phosphatase (ALP) had been reported to be increased in alloxan-induced diabetic rats, [29]. Increased in serum liver enzymes parameters in diabetic control group observed in the present investigation corroborates these findings. Reduction in liver enzyme levels in group 3 (1g, C.F.S.D.) and 4 (2g C.F.S.D.) clearly indicates the therapeutic role of *Capsicum frutescens* against increased in serum liver enzyme parameters correlated with alloxan induced diabetes. In previous research, *Capsicum frutescens* had been documented to protect against iron overload liver injury by reducing plasma liver parameters level to normal, [16].

There was a significant increase in serum creatinine level of group 2. An increase in plasma creatinine levels may be a sign of impaired renal function which is associated with diabetes. The elevation in the plasma creatinine concentration indirectly suggests kidney damage specifically the renal filtration mechanism, [30]. Significant reduction observed in the serum creatinine levels of the diabetic rats treated with 1g and 2g C.F.S.D in this study suggests

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protective effect by *Capsicum frutescens* against kidney disorders associated with diabetes mellitus.

4. CONCLUSION

In this study, increase in serum liver enzymes (AST, ALT, ALP, GGT), increased in serum uric acid, creatinine, total cholesterol, fasting blood glucose level and reduced high density lipoprotein (HDL) cholesterol associated with alloxan induced diabetes mellitus were ~~reversed~~ ameliorated after ~~treatment~~ treated with 1g and 2g Capsicum frutescens supplemented diet. ~~Such remarkable changes observed in this study could be traced to the active ingredients [capsaicin, dihydrocapsaincin, antioxidant vitamins (ascorbic acid, vitamin E), carotenoids (β-carotene, β- cryptoxanthine) and several organic acids and minerals present in *Capsicum frutescens*.The thermogenic properties of capsaicin found in red pepper has been reported by several authors and results from this study also lends credence to that fact. It's therefore recommended that *Capsicum frutescens* be added as spices to the food of obese individual as well as diabetic patients for its hypoglycemic properties, inducing of increase energy utilization as well as being cardio-protective by its effect on plasma lipids.~~ The results indicated that *Capsicum frutescens*, as spice in the diet, is benefits for the diabetic patients.

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AUTHORS' CONTRIBUTIONS

Author 1 designed the study and wrote the first draft of the manuscript. Author 2 managed the literature searches; author 3 performed the statistical analysis and managed the analyses of the study. All authors read and approved the final manuscript.

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