



Effect of Epigallocatechin Gallate on Metabolic Enzymes Activity in Streptozotocin-induced Zebrafish Model of Diabetes

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ABSTRACT

Background: The therapeutic potential of naturally occurring flavonoids, particularly in managing diabetes-related complications, has garnered significant attention. This study explores the impact of epigallocatechin gallate (EGCG), a bioactive compound found in green tea, on the activity of key metabolic enzymes like alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) in the liver, gills and kidneys of zebrafish. The experimental design included four groups: Control, diabetic, diabetic treated with EGCG and control treated with EGCG, with enzyme activities assessed on days 1, 7, 14 and 21.

Methods: Zebrafish were categorized into four groups: control, diabetic, diabetic administered EGCG and control administered EGCG. Enzyme activity of ALT, AST and ALP in liver, gill and kidney tissues were assessed on days 1, 7, 14 and 21.

Result: The diabetic group demonstrated a substantial elevation in ALT, AST and ALP activities in all tissues, with ALT activity increased by 30.67% in the liver, 39.67% in the gills and 5.39% in the kidneys on day 21 relative to the control group. EGCG administration in the diabetic group markedly decreased metabolic enzyme activity, signifying a therapeutic impact. Analogous trends were noted for AST and ALP, indicating the therapeutic efficacy of EGCG in addressing diabetes-related metabolic disorders. EGCG exhibits potential as a protective agent with practically curative effects in a streptozotocin-induced diabetic zebrafish model, highlighting its ability to alleviate diabetes-related complications.

Key words: Alanine aminotransferase, Alkaline phosphatase, Aspartate aminotransferase, Diabetes, Epigallocatechin gallate, Zebrafish.

INTRODUCTION

Diabetes mellitus (DM) has emerged as a major metabolic illness marked by increased blood glucose levels resulting from impaired insulin production or insulin receptor activity. Environmental and genetic variables affect the etiopathogenesis of the disease, with global forecasts anticipating an increase in cases to around 642 million by 2040 (Dendup *et al.*, 2018). This results in intricate metabolic and biochemical disturbances that induce functional impairments in biomolecular systems, especially under hyperglycemic conditions that facilitate the formation of advanced glycation end products and the generation of reactive oxygen species. Complications from chronic diabetes mellitus are common and include changes in blood parameters (Pankaj and Varma, 2013) and reproductive dysfunctions (Pankaj, 2015). Furthermore, Devi *et al.* (2016) and Singh *et al.* (2016) found that it is linked to sexual dysfunctions in both diabetes men and women.

Research on DM processes and therapeutics utilises several animal models, particularly zebrafish, which are proficient for studying DM through Streptozotocin (STZ)-induced β -cell apoptosis, hence replicating DM pathogenesis (Longkumer *et al.*, 2020, 2022). Catechins in green tea (*Camellia sinensis*) helps in reducing the chance of developing DM. EGCG has been demonstrated to enhance insulin responsiveness, increase glucose tolerance and guard against oxidative stress-induced cell death in diabetic models. Aloe vera juice has been shown to lower blood sugar levels in diabetic animals (Pankaj, 2011) and

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Priyadarshani *et al.* (2011) found that the leaves of the *Moringa oleifera* lowered cholesterol levels in diabetic mice. Singh *et al.* (2019) assessed effects of green tea extract on the testicles of diabetic rats. Additionally, the function of EGCG in facilitating caudal fin regeneration in diabetic zebrafish was examined by Jamir *et al.* (2023) and its ability to alleviate oxidative stress and restore histological integrity in diabetic zebrafish has been recorded by Jamir *et al.* (2024a).

Metabolic enzymes, including ALT, AST and ALP, serve as crucial indicators of metabolic health, particularly under diabetic stress and are associated with non-alcoholic fatty liver disease (Amjad *et al.*, 2018). Alterations in the specified enzyme activities function as biomarkers that signify cellular

metabolic alterations, therefore offering diagnostic insights into health status and organ damage resulting from DM stress. Additional research is necessary due to the little existing evidence regarding effects of EGCG on metabolic enzymes in diabetes-induced zebrafish. This work investigates the interactions of EGCG with ALT, AST and ALP in the liver, kidney and gills of zebrafish subjected to STZ-induced diabetes to assess potential of EGCG in alleviating diabetes-induced metabolic disturbances (Jamir, 2024b).

MATERIALS AND METHODS

Chemicals and reagents

EGCG was sourced from Merck and metabolic enzyme kits from ERBA Chemicals (Erba Diagnostics, Germany). The assays were performed using the Benesphera C61 semi-automatic biochemical analyzer.

Experimental animals

Adult zebrafish (*Danio rerio*), aged 3-5 months and measuring 3-5 cm, were obtained from "Aqua Fish and Pets" in Jorhat, Assam, India. They were housed at $28 \pm 2^\circ\text{C}$ in a controlled environment with proper filtration and aeration ($7.20 \text{ mg O}_2/\text{L}$). Before the experiment, fish were treated briefly with 0.05% KMnO₄ to prevent infections and maintained under a 14-hour light/10-hour dark cycle. Only healthy, active fish were selected for the study.

Study design

Zebrafish were divided into four groups (n=6): Group I (control), Group II (diabetic), Group III (diabetic+EGCG) and Group IV (control+EGCG). Groups III and IV were exposed to 6 mg/L of EGCG throughout the experiment.

Induction of diabetes

Diabetes was induced by intraperitoneal injection of STZ (0.35 mg/g body weight) with five booster doses over 21 days, as per Longkumer *et al.* (2020, 2024).

Tissue preparation

Liver, gill and kidney tissues were dissected and homogenized (2.5% w/v) in cold KCl-phosphate buffer (pH 7.4), then centrifuged at 2000 rpm for 15 minutes at 4°C . The resulting supernatant was used for biochemical analyses. Euthanasia was performed using a recommended dose of tricaine methanesulfonate (MS-222), in accordance with ethical guidelines.

Biochemical analysis

ALT, AST and ALP levels were measured using the ERBA kit following the manufacturer's instructions.

Statistical analysis

Data were analyzed using GraphPad Prism 5 and presented as mean $\pm$ SD. One-way ANOVA and Tukey's post hoc test were applied (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

RESULTS AND DISCUSSION

Hepatic ALT and AST activity

During the 21-day study period, hepatic ALT and AST activity of diabetic group significantly ($p < 0.05$) increased in comparison to group I. Specifically, on day 21, AST activity clearly increased by 59.33%, while ALT levels increased from 25.34% to 30.67%. In contrast, ALT activity of group III gradually decreased over the course of the 21-day treatment period, reaching 110.68 ± 2.16 on day 21. Simultaneously, AST activity decreased on day 21 data showed 28.83 ± 2.63 . There were insignificant differences ($p > 0.05$) in the hepatic ALT and AST activity between group I and group IV, indicating a similar enzymatic profile. The hepatic ALT and AST activity of experimental zebrafish variations throughout time are showed in Fig 1 and 2.

ALT and AST activity in gills tissue

The ALT activity in the gill tissue of diabetic group was significantly ($p < 0.05$) higher than that of group I, with increases of 31.35%, 35.67%, 37.84% and 39.67% on days

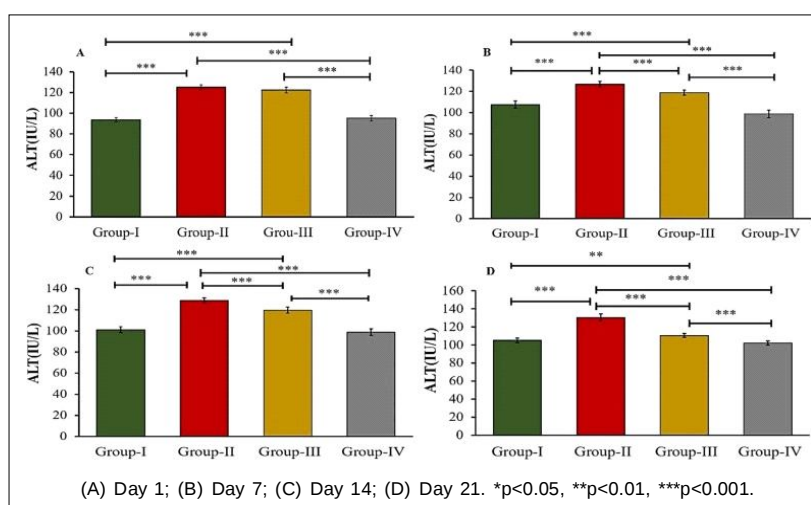


Fig 1: Effect of diabetes on the hepatic ALT activity in the experimental zebrafish.

1, 7, 14 and 21, respectively. In addition, AST activity of diabetic group increased significantly by 54.66% on day 21. However, ALT and AST levels consistently decreased in group III, confirming the that EGCG had a protective effect against cellular damage. There were insignificant differences ($p>0.05$) in the ALT and AST activities, indicating that the enzymatic processes in group I and Group IV were similar. The ALT and AST activity in gill tissue throughout the experimental days is shown in Fig 3 and 4.

ALT and AST activity of renal tissue

Diabetic group demonstrated a significant increase in ALT and AST activity of kidney tissues, with increases of 11.66%, 9.83%, 7.83% and 5.34% recorded on days 1, 7, 14 and 21, respectively, in comparison to group I for ALT. The group-II subjects exhibited a significant increase in AST activity, with rises of 58.83% and 54.83% on days 14 and 21, respectively. Group III demonstrated a substantial reduction in AST activity ($p<0.001$) across the 21-day treatment period, with values of 77.34 ± 2.16 for ALT on day 21 and 69.33%

and 71.83% on days 14 and 21, respectively, in comparison to diabetic group for ALT. Additionally, statistically insignificant values ($p>0.05$) were noted between test group I and group IV. Fig 5 and 6 depict the AST activity in renal tissue over experimental days.

ALP activity of hepatic and renal

ALP activity, an indicator of genotoxic and cytotoxic stress, was substantially elevated in the liver and kidneys of diabetic group. The liver showed increases of up to 56.83% and the kidneys up to 72.16. Additionally, group III exhibited a significant decrease in hepatic ALP activity throughout the 21-day treatment duration, with values declining to 72.84% on day 21 for hepatic ALP and demonstrating an 84.16% drop on day 21 compared to diabetic group for renal ALP. The ALP activities were deemed insignificant ($p>0.05$) between group I and group IV. Fig 7 and 8 depict the ALP activity in the hepatic and renal tissues of the experimental zebrafish throughout several days.

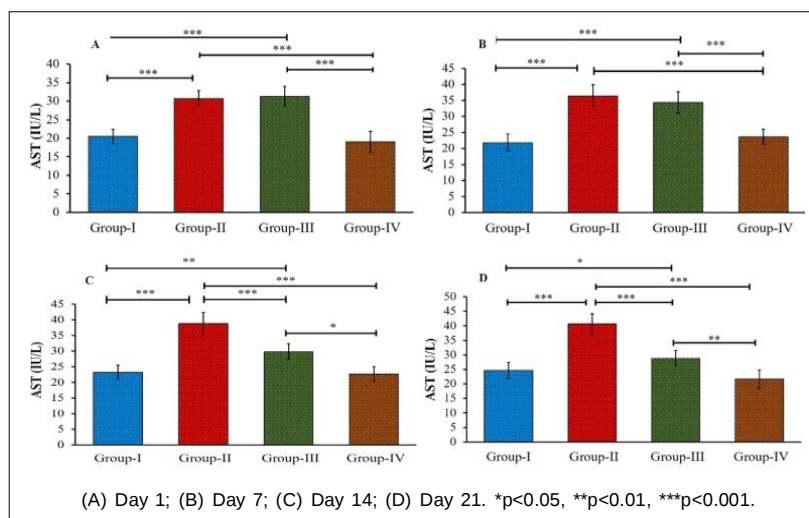


Fig 2: Effect of diabetes on hepatic AST activity in the experimental zebrafish.

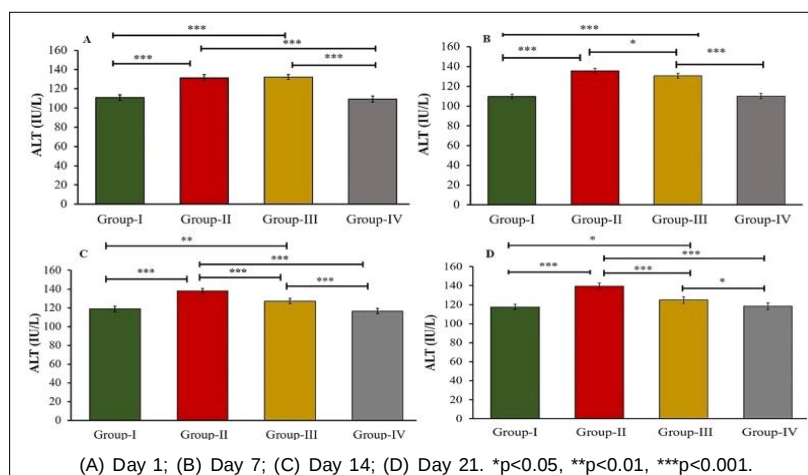


Fig 3: Effect of diabetes on the gills ALT activity in the experimental zebrafish.

DM is a disease that can lead to difficulties since it affects several organs and makes it difficult to control blood sugar. Because streptozotocin (STZ) specifically destroys pancreatic β -cells, causing oxidative and metabolic stress, it is mainly used to induce diabetes in animal models (Amirkhosravi *et al.*, 2023). The zebrafish model accurately reflects human diabetes pathophysiology, therefore rendering it an appropriate model for research. Its physiological resemblances to humans regarding pancreatic shape, lipid metabolism, glucose balance and adipose tissue physiology further substantiate its suitability for experimental research (Jamir *et al.*, 2024b).

Building on this established model, our study focused on evaluating the therapeutic efficacy of natural compounds, specifically epigallocatechin gallate (EGCG), in mitigating diabetes-induced metabolic disturbances. The therapeutic potential of natural bioactive compounds in managing diabetes and its associated complications has been widely explored (Pankaj, 2016). Increasingly, researchers are turning to

plant-derived compounds such as EGCG due to their safety profile and antioxidant properties, as opposed to synthetic drugs. EGCG has been demonstrated to alleviate oxidative stress and immune-related damage caused by various toxic agents (Samim and Vaseem, 2023; Jamir *et al.*, 2024a).

Hepatic enzymes like ALT and AST play an important role in diabetes. The current investigation revealed markedly increased ALT and AST activity in the hepatic tissue of diabetic zebrafish, indicating hepatic impairment and metabolic disturbance in the Krebs cycle, resulting in enzyme leakage into the circulatory system (Bojarski and Witeska, 2020). These findings coincide with the results of Amirkhosravi *et al.* (2023), who followed high blood ALT and AST levels among diabetic rats.

Group III showed a notable decline in liver ALP activity across the 21-day treatment period; by day 21, this decline was 72.84%. Indicating that EGCG may have a protective effect, Group III displayed a comparable 84.16% decline in kidney ALP when compared to diabetic group. Kidneys and gills of diabetic zebrafish revealed increased amounts

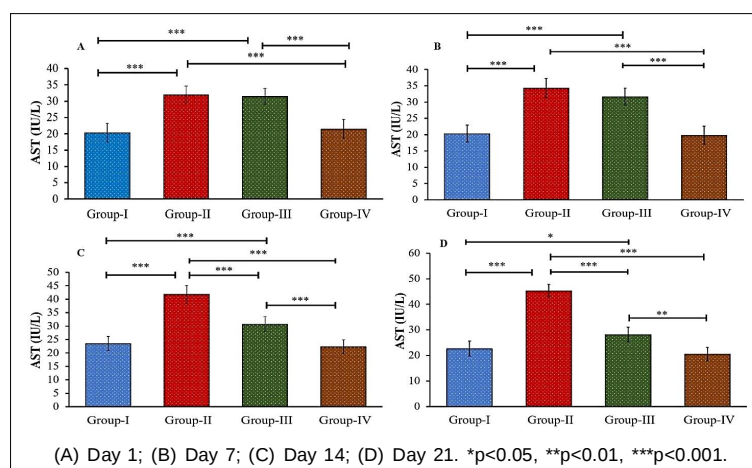


Fig 4: Effect of diabetes on gills AST activity in the experimental zebrafish.

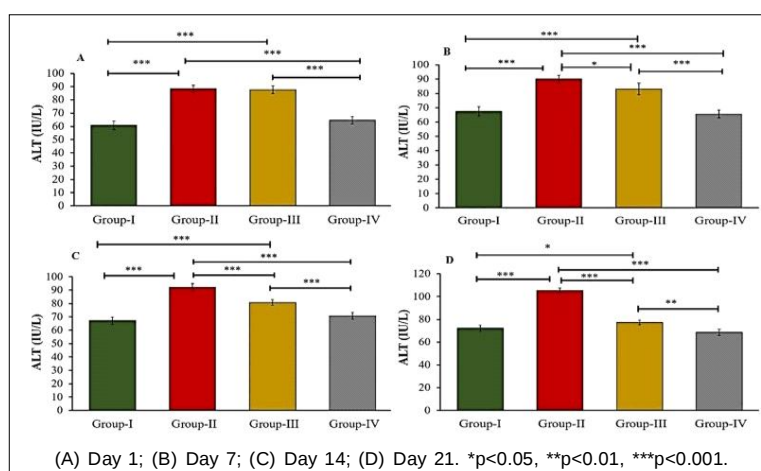


Fig 5: Effect of diabetes on renal ALT activity in the experimental zebrafish.

of ALT and AST, according to the study. This implies that damage induced by reactive oxygen species (ROS) most likely explains the malfunction of the mitochondria allowing dangerous substances to enter (Wang *et al.*, 2022). Similar changes in metabolism have been seen in zebrafish studies. Active transamination is an important part of how energy is processed in these fish (Samanta *et al.*, 2014).

Khajuria *et al.* (2018) examined the hepatoprotective effects of Seabuckthorn leaf extract (SLE) in Streptozotocin (STZ)-induced diabetic rats, observing significant enhancements in serum enzyme levels (AST, ALT, ALP and ACP) in the SLE-treated group relative to the diabetic control, thereby indicating hepatoprotection. Chandnani *et al.* (2022) evaluated the therapeutic efficacy of biosynthesized silver nanoparticles in a diabetic rat wound model, with the objective of comparing wound healing outcomes in diabetic rats. Shahid *et al.* (2019) investigated the anti-diabetic effects of *Nelumbo nucifera* leaves, revealing that the butanol fraction markedly lowered blood

glucose levels in Alloxan-induced diabetic rabbits, indicating its potential as an anti-diabetic treatment. Divya *et al.* (2016) assessed the antioxidant efficacy of *Terminalia catappa* leaf extract in STZ-induced diabetes, demonstrating that the ethanolic extract markedly elevated antioxidant levels, with the 500 mg/kg dosage providing optimal protection against oxidative stress, suggesting its potential in mitigating diabetes-related oxidative damage.

Moreover, elevated ALP activity in the liver and kidney of diabetic zebrafish suggests genotoxic and cytotoxic consequences, aligning with studies carried out by (Samanta *et al.*, 2014). The addition of EGCG significantly restored enzyme activity, showing its protective role against organ damage. EGCG is well-known for its ability to protect the liver from toxins (Parasuraman *et al.*, 2021) and has shown promise in reducing kidney inflammation and organ damage in diabetes rats (Yang *et al.*, 2022, Jamir, 2024). Changes in ALT, AST and ALP levels after EGCG hint to it maybe being a helpful early treatment for diabetes-related issues. These results indicate that zebrafish offer a basis

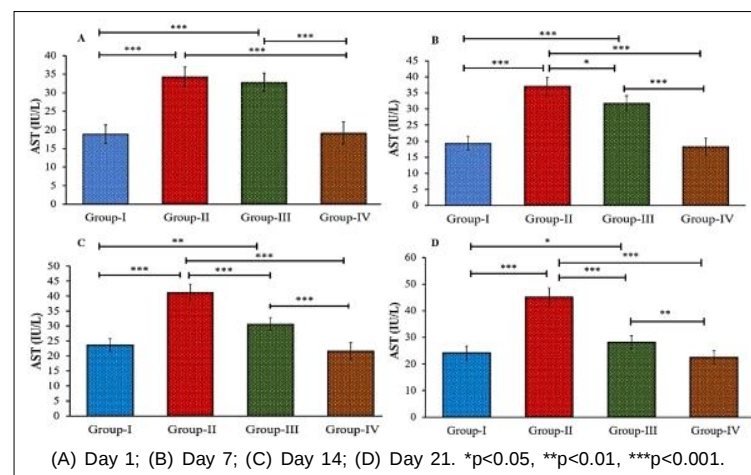


Fig 6: Effect of diabetes on renal AST activity in the experimental zebrafish.

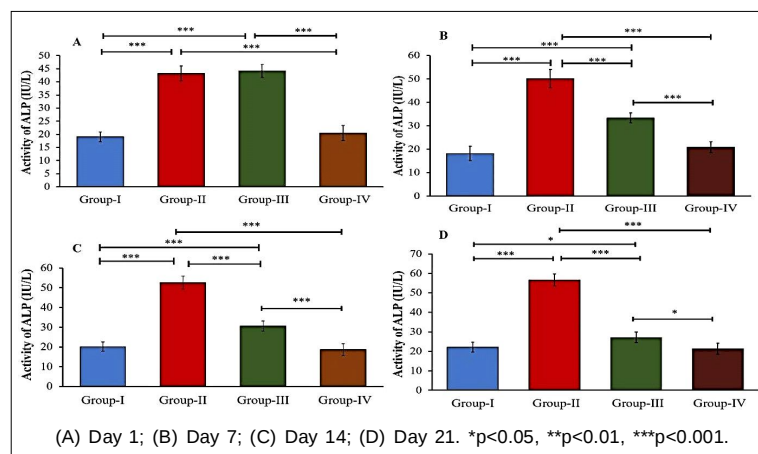


Fig 7: Effect of diabetes on hepatic ALP activity in the experimental zebrafish.

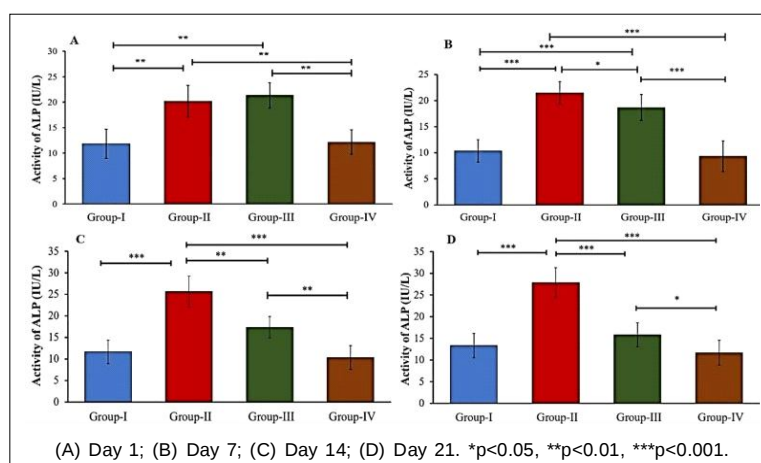


Fig 8: Effect of diabetes on renal ALP activity in the experimental zebrafish.

for investigating how EGCG functions as a medication and help to investigate metabolic illnesses. Future research should focus on elucidating how EGCG works in the body to stop diabetes harm. This will let it be transferred from a lab setting to a possible diabetic cure.

CONCLUSION

Our study unequivocally demonstrates that diabetes induced in zebrafish via STZ results in significant and measurable alterations in enzyme activity, profoundly affecting the liver, gill and kidney tissues and thereby compromising the overall health of the test subjects. These findings highlight the potential of EGCG as a potent ameliorating agent capable of restoring disrupted enzyme activity, reinforcing its promise as a therapeutic candidate for managing diabetic complications. Furthermore, the study comprehensively explores the underlying mechanisms of protective effects of EGCG. However, certain limitations remain, including the lack of oxidative stress biomarker analysis. Despite this, the results offer promising translational relevance for the therapeutic application of EGCG in diabetic conditions.

Ethics approval

The experimental animal protocols were approved by the Institutional Animal Ethics Committee (IAEC) under IAEC approval no. NU/ZOO/IAEC/Meeting No. 1/2020, Protocol No. 4.

Declaration

This research paper is based on Ajungla Jamir's PhD thesis, which was completed under Pranay Punj Pankaj's guidance. The Shodhganga@INFLIBNET Centre is the archive for the thesis. For further reference, please see: Jamir, A. (2024). Efficacy of green tea polyphenol epigallocatechin gallate (EGCG) for the management of diabetes mellitus in zebrafish model (Doctoral dissertation, Nagaland University, Department of Zoology). Nagaland University. <http://hdl.handle.net/10603/615224>.

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Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All animal procedures for experiments were approved by the Committee of Experimental Animal care and handling techniques were approved by the University of Animal Care Committee.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish or preparation of the manuscript.

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