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Effect of zonisamide and *Nigella sativa* combination in traumatic brain injury-induced hyperglycemia and hypertension

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Abstract
Traumatic brain injury is a widespread public health threat that has resulted in millions of deaths and disabilities worldwide. Numerous medicines available provide symptomatic relief but do not stop secondary injury from progressing. Hence, innovative therapeutic agents that protect against neuronal damage following trauma and its associated complications, particularly secondary injury, are needed. The study used a Swiss albino mouse (25-30 g) of either sex. Traumatic brain injury was induced by a weight-drop model, and blood glucose level and systolic blood pressure were observed at different time intervals. The parameters (blood glucose and Systolic blood pressure) were significantly reduced by treatment with zonisamide and *Nigella sativa* per se and in combination. Comparatively, low blood glucose levels and Systolic blood pressure were observed when zonisamide (100 mg/kg) and NS (300 mg/kg) were co-administered, indicating the potential role of both drugs in the prevention of TBI-induced hyperglycemia and hypertension.

Keywords: blood glucose, hyperglycemia, *nigella sativa*, systolic blood pressure, traumatic brain injury, zonisamide

Introduction
Traumatic brain injury (TBI) is a serious health concern. Over 5 million people in the United States have secondary TBI-related disabilities. [15] Noteworthy, rising evidence suggests that suitable early management of TBI may improve patient outcomes by averting or diminishing secondary brain injuries [10]. TBI boosts several vital and efficient modifications that consequently worsen a patient's condition, as revealed by numerous clinical and investigational studies [2]. Because of limited medicines for the effective prevention of primary head injury, the slants for traumatic head injury treatment are now focused on averting secondary damages [19].
Zonisamide is a novel broad-spectrum antiepileptic drug that works well for refractory partial seizures. Zonisamide has a structural, molecular, and pharmacokinetic profile apart from other antiepileptic drugs. [18] Moreover, it does not have any adverse cardiovascular side effects and has also been found responsible for reducing blood pressure (BP) and heart rate (HR) [6, 7].
Recently, plants and herbs' low toxicity and cost-effectiveness have gained attention to investigate their potential pharmacological activities. *Nigella sativa* (NS) is an herb belonging to the family Ranunculaceae, and its seeds are conventionally used to treat various diseases around the globe [23]. Several clinical and animal studies affirmed that NS and its active component, thymoquinone, exhibit potential antioxidative [12] immunomodulatory [1], neuroprotective [11], antibacterial [5], antihypertensive, and hypoglycaemic [24] effects.
Assuredly, the management of hyperglycemia during acute TBI in adults can help to generate better outcomes [22] and will play a significant feature in the management of head injuries [16]. Likewise, systolic blood pressure (SBP) also has a contributing role in the secondary injury cascade after severe traumatic brain injury, and its management can be an add-on to the better management of trauma-induced brain injuries [14]. The present research aims to provide an underline effect of zonisamide and NS combination in the management of hyperglycemia and hypertension after TBI in mice.

Materials and Methods
Animal
The study used a Swiss albino mouse (25-30 g) of either sex, kept under natural day and night cycles in polypropylene cages with rodent food and water ad libitum. All experimental procedures were approved by the Institutional Animal Ethics Committee at Maharshi Dayanand University in Rohtak, Haryana, India.

Induction of TBI by weight drop method

Mice were anesthetized with 2% isoflurane and allowed to breathe naturally without tracheal intubation. After that, mice were placed on a sponge using surgical tape, and a small longitudinal incision was given to the overhead of mice exposed to the skull. The metallic disc was centrally fixed on the exposed skull and adequately placed the mice under the metallic pipe. Then the metallic spherical weight (60 gm) freely falls through the metallic pipe over the head of the mice. After that metallic disc was removed and sutured to enclose the exposed skull. Finally, Neosporin powder was spread over the surgery site and then returned to its home case for recovery.

Treatment schedule

The experimental study was designed to determine blood glucose and SBP level at different time intervals. The drug was administered 30 min after the induction of TBI. Mice were divided into five groups, each consisting of 6 mice. Group 1, the control group, did not receive any injury or drug treatment, whereas TBI was induced in all other four groups. Group 2 received TBI + Vehicle, Group 3 received TBI + zonisamide 100 mg/kg, Group 4 received TBI +NS 300 mg/kg, group 5 received TBI + combination of zonisamide 100 mg/kg and NS 300 mg/kg.

Measuring blood glucose concentrations using a glucometer

Aquacheck glucometer was used to measure the blood glucose level in mice. After restraining, the mice's tail was needle-pricked and massaged gently from the base upward to collect the blood droplet. The obtained droplet was placed on a glucose strip placed inside a handheld glucometer. [13] Blood glucose level was measured after 0.25, 0.5,1,2,4,24 and 72 h after drug administration.

Measuring SBP by the tail-cuff method

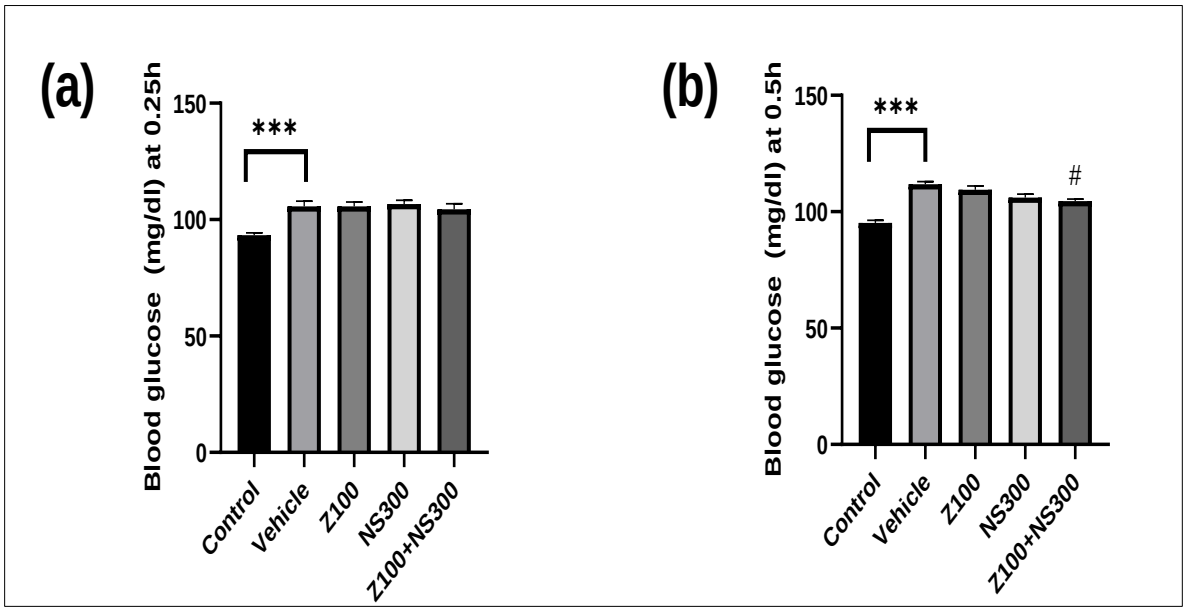
The noninvasive blood pressure acquisition system (AD instruments), based upon the volume pressure recording (VPR) technique, was employed for tail-cuff measurements of SBP in mice at different time intervals. The experiment was conducted in a selected noiseless area (22±2°C), where mice were acclimatized for a 10 min period before the commencement of experiments. All mice were fortified to be restrained in specifically designed restraint tubes to avoid excessive movement.

The occlusion cuff was positioned at the base of the tail. After that, the sensor cuff was placed adjoining the occlusion cuff. The occlusion cuff was inflated up to 250 mm Hg and deflated over 20 s to measure blood pressure. The VPR sensor cuff senses tail volume variations as the blood flow back to the tail during the occlusion cuff deflation, and BP was recorded. The SBP obtained on the recording device was noted down. Each recording session consisted of 10 to 15 inflation and deflation cycles per set.

Results

Effect of zonisamide and NS on blood glucose level

The blood glucose level of mice observed at 0.25, 0.1, 1, 2, 4, 24, and 72h are described in Figure 1. Compared to the control group, the blood glucose level significantly amplified in the vehicle-treated group at all-time intervals. Zonisamide and NS-treated groups demonstrated a considerable reduction in the blood glucose level at all-time intervals. Comparatively, low blood glucose level was observed when both zonisamide (100 mg/kg) and NS (300 mg/kg) were co-administered. Although, at 72h, the blood glucose level of the co-administered group showed no significant difference compared to the control group.



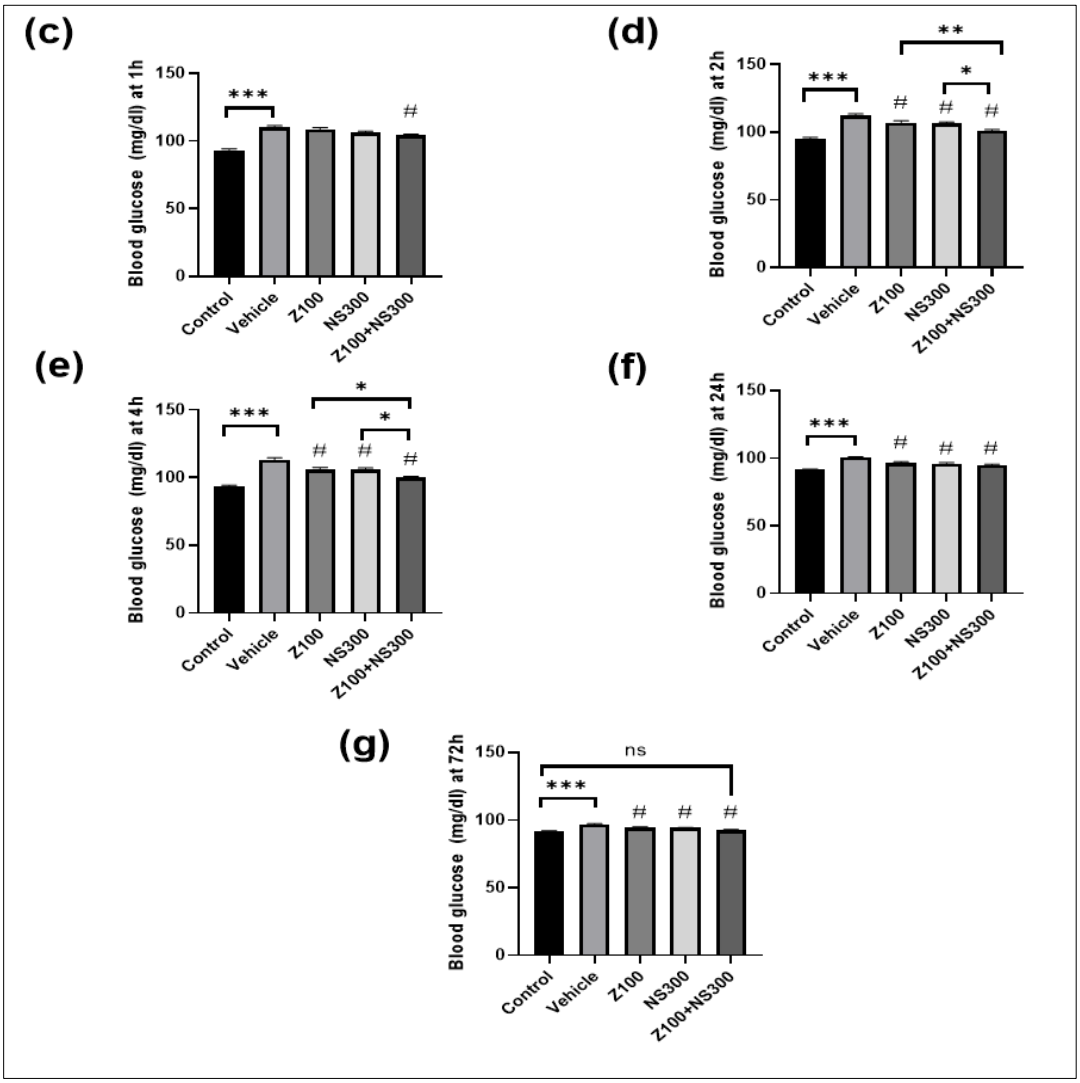
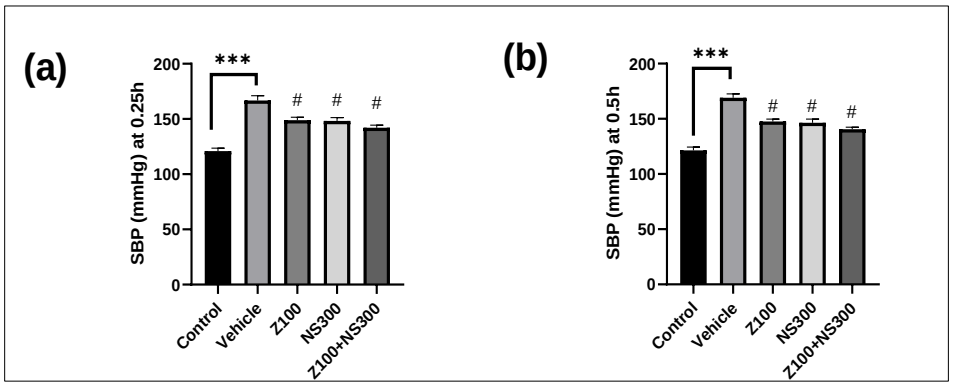


Fig 1: Effect of zonisamide, NS, and its combination on (a) Blood glucose at 0.25h, (b) Blood glucose at 0.5h (c) Blood glucose at 1h, (d) Blood glucose at 2h (e) Blood glucose at 4h (f) Blood glucose at 24h, and (g) Blood glucose at 72h in mice.

The data were analyzed using one-way ANOVA, followed by Bonferroni's multiple comparison tests. Data were denoted as mean ±SEM and statistical significance denoted as *, ** or *** for $p < 0.05$, 0.01, and 0.001, respectively. p values were shown with '#' representing $p < 0.05$ when compared with vehicle.

Effect of zonisamide and NS on SBP

The Systolic blood pressure (SBP) of mice was observed at 0.25, 0.1, 1, 2, 4, 24, and 72h and are illustrated in Figure 2. Compared to the control group, the SBP was significantly augmented in the vehicle-treated group at all-time intervals. Zonisamide and NS-treated groups demonstrated a considerable decrease in the SBP at all-time intervals. However, comparatively low SBP was observed when both zonisamide (100 mg/kg) and NS (300 mg/kg) were co-administered. Noteworthy, no significant difference in SBP was observed at 72h in all treatment groups.



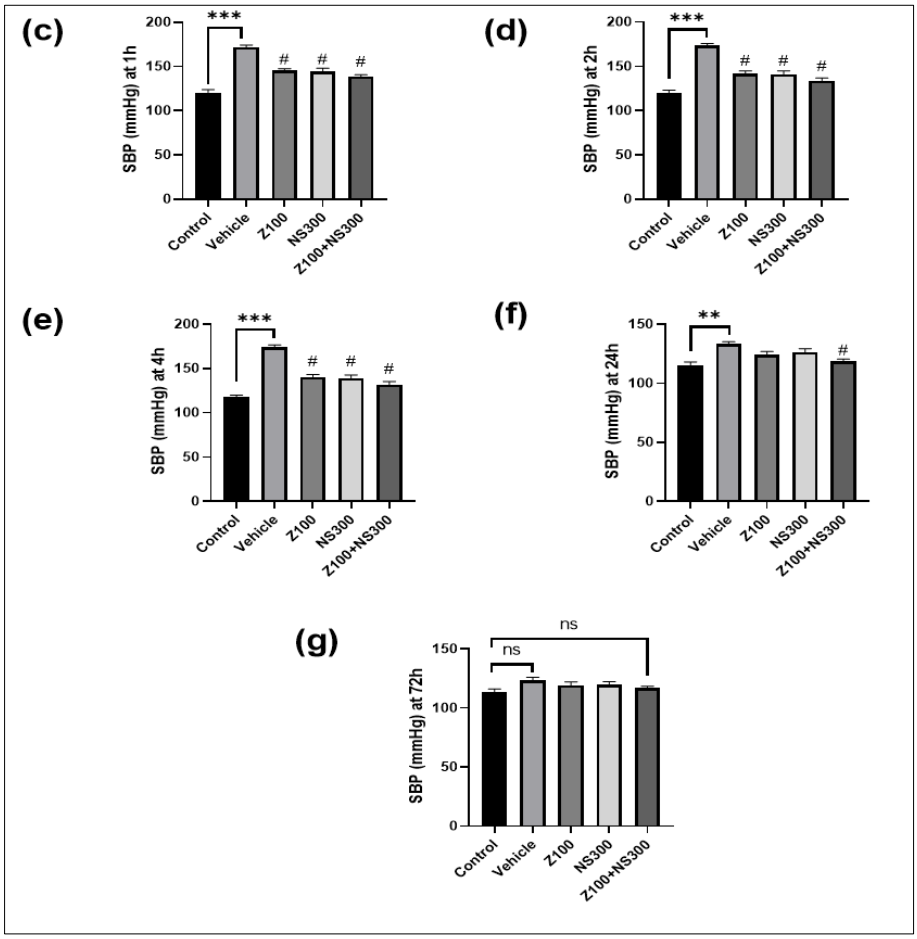


Fig 2: Effect of zonisamide, NS and its combination on (a) SBP at 0.25h, (b) SBP at 0.5h. (c) SBP at 1h, (d) SBP at 2h (e) SBP at 4h (f) SBP at 24h and (g) SBP at 72h in mice.

The data were analyzed using one-way ANOVA, followed by Bonferroni's multiple comparison tests. Data were denoted as mean ±SEM, and statistical significance was denoted as** or *** for $p < 0.01$, and 0.001, respectively. p values were shown with '#' representing $p < 0.05$ when compared with vehicle.

Discussion

TBI is a growing health menace and is the foremost reason for mortality in young adults, with an average of 3.5 times more death rate than cancer and other heart-related diseases. [8] Hyperglycaemia is one of the most common TBI-associated secondary complications allied with poor clinical outcomes and is accountable for amplifying congestive heart failure, cardiogenic shock, and even death. A prospective randomized human study revealed that TBI patients with persistent hyperglycemia have a considerably high disability and fatality rates. [4] Furthermore, in another study, patients with raised blood glucose levels experienced a remarkably greater incidence of infections and extended hospitalization. [3] Predominantly, several investigations have developed an interconnection between blood glucose levels and its outcomes in patients hospitalized with TBI [9].

Similarly, the pathophysiologic effect of elevated BP on neurophysiologic mechanisms after TBI is multifaceted and includes a relationship between systemic blood pressure, intracranial pressure (ICP), cerebral edema, and cerebral autoregulation [21]. During normal physiology, cerebrovascular autoregulatory mechanisms are accountable for constant cerebral blood flow, regardless of any alteration in systemic blood pressure. [17] However, in the traumatized brain, these autoregulatory mechanisms get impaired, and elevation in systemic blood pressure triggers the blood flows in cerebral capillaries, causing a remarkable increase in ICP, worsening cerebral edema, which consequently collapses the blood-brain barrier [20].

In the current investigation, the altered blood glucose level and SBP were significantly reduced by treatment with zonisamide and NS per se and in combination.

Conclusion

Elevated glucose levels and SBP are critical pathophysiological markers of TBI, and their management helps prevent further TBI- triggered secondary outcomes. Still, rare stress is given to their management. Intervention with zonisamide and NS per se and, in combination, improved these alterations. So, from the above findings, it can be concluded that co-administration of zonisamide and NS can be used to manage these TBI-induced consequences.

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