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t-AUCB Improves Endothelial Function and Maintains Liver-Kidney Function in Mouse Model of Polymicrobial Sepsis

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Abstract

Endothelial dysfunction associated with multiple organ failure predominantly leads to poor prognosis and high mortality in septic patients. Stabilisation of epoxyeicosatrienoic acids (EETs) levels via inhibiting their breakdown by the soluble epoxide hydrolase (sEH) enzyme was reported to be beneficial in various inflammatory conditions. The current investigation elucidates the impact of *in vivo* administration of t-AUCB (a potent sEH inhibitor) on endothelium-dependent and -independent vasorelaxation in the mouse aorta, along with its impact on liver-kidney biomarkers in septic mice. Marked endothelial dysfunction, as evidenced by a reduction in relaxant response to acetylcholine (ACh) was found in septic mice, while endothelial-independent relaxation to sodium nitroprusside (SNP) remains unaltered. Significantly elevated serum levels of liver and kidney biomarkers like alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN) and creatinine in septic mice as compared to SO mice were found. Treatment of septic mice with t-AUCB and/or with imipenem (IMI) improved endothelial vasorelaxation to ACh, while endothelium-independent vasorelaxation to SNP remained unaltered. Further, t-AUCB alone and/or with IMI also restored the elevated levels of liver and kidney biomarkers. Thus, the sEH inhibitor, t-AUCB, helps to improve vascular endothelial dysfunction and consequently liver and kidney dysfunction in sepsis, possibly via regulating circulatory perfusion.

Major Findings: sEH inhibitor, t-AUCB, improves endothelial function and exerts organ protective effect in sepsis possibly by regulating circulatory perfusion and inflammatory cascade.

Keywords: Endothelium, Imipenem, Sepsis, Soluble Epoxide Hydrolase, t-AUCB

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1. Introduction

Sepsis, a dysregulated host response to infection, is associated with acute multi-organ dysfunction and a high risk of death[1]. The incidence of sepsis is high, with an estimate of 20% of all global deaths[1] and 52% of hospital mortality[2]. Cytokine storm accompanied by activation of the complement system and endothelial cells during sepsis culminates in microcirculatory disturbances leading to multi-organ failure[3]. Microcirculatory disturbances often envisage cellular components of circulation, *viz.*, leukocytes, red blood cells, platelets, endothelial cells, smooth muscle cells, and the adjoining parenchymal cells[4]. The commonly observed manifestations of disturbed microcirculation are persistent

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hypotension, peripheral resistance to vasoconstrictor (vasoplegia) and endothelial dysfunction[5-6]. Endothelial dysfunction occurs due to glycocalyx destruction, dysregulation of nitric oxide (NO), impaired cellular communication, oxidative damage, activation of adhesion molecules and damage due to inflammatory mediators[5-6]. This eventually leads to circulatory disturbances to various tissues, leading to oedema, hypoperfusion and multiple organ failure[7-8]. Therefore, therapeutic strategies aimed to restore or preserve endothelial function using anti-inflammatory agents, antioxidants, and endothelial protective agents were found to be beneficial in various inflammatory conditions and are even positively correlated with prognosis in septic patients[7,9,10].

Epoxyeicosatrienoic acids (EETs) generated via oxidative metabolism of arachidonic acid have a role in regulating blood pressure and inflammation[11-13]. Moreover, they are well known for their anti-inflammatory[11], cardio-protective and other organ protective effects[14-15]. However, they are rapidly metabolised to dihydroxyeicosatrienoic acids (DHETs) by the enzyme soluble epoxide hydrolase (sEH)[14]. Thus, maintaining EET levels via inhibiting sEH activity either by pharmacological agents or by genetic means was reported to be beneficial in experimental studies of hypertension[12], diabetes[16,17], liver diseases[18], acute lung injury[19], as well as in endotoxemia[13,20,21]. The observed effects following sEH inhibition in various inflammatory conditions were attributed to either an increase in EET levels or EET: diol ratio[13], reduction in production of proinflammatory molecules[13,21] or by regulating macrophage function[22]. Although beneficial effects of EET in sepsis were reported, most of these studies were done using an endotoxemic model of sepsis[11,13,19,22]. Moreover, the effect of prophylactic administration of sEH inhibitor on sepsis outcomes in the caecal ligation and puncture (CLP) model of sepsis has also been reported[20,21]. However, the therapeutic benefit of sEH inhibition, if any, on endothelial dysfunction and blood vessel relaxation in polymicrobial sepsis is yet to be explored. So, herein we assessed the effect of *in vivo* administration of t-AUCB on endothelium-dependent and -independent vascular response and associated biochemical alterations in the late phase of sepsis.

2. Materials and Methods

2.1 Animal Acquisition and Maintenance

The present investigation was carried out in adult male Swiss albino mice (25-30 g) obtained from "Disease Free Small Animal House (DFSAH), College of Veterinary Science, LUVAS, Hisar, India". Mice were maintained in controlled environment (temperature: 23–25 °C and humidity: 50%) in the Laboratory Animal House with 12 h light-dark cycle. Prior to experiments, all the animals were acclimatised for a period of one week. A balanced food (procured from Ashirwad Industries, Mohali, Punjab, India) and water were supplied during the entire experimental period. All the care, maintenance of the animals and the experiments were done following ethical standards with approval from the Institutional Animal Ethics Committee (IAEC) (Approval No.: IAEC/20/8 via letter No. 131/IAEC/20 Dated 30.12.2020).

2.2 Caecal Ligation and Puncture in Mice

Polymicrobial sepsis in mice was induced by the CLP method as described earlier[23]. Before surgery, *ad libitum* water was supplied to mice, but food was restricted for overnight. By anaesthetising with xylazine (10 mg/kg b.wt, *i.p.*) and ketamine (80 mg/kg b.wt, *i.p.*), about 1 cm midline incision was made on the ventral side of the abdomen of the mouse. The cecum was carefully isolated and tied with 2–0 silk suture just distal to the ileocecal bifurcation without affecting the patency of the intestinal lumen. Thereafter, two punctures were made on the caecum using a 21G sterile needle and placed back into the abdominal cavity. The incision line was closed aseptically. To reduce the chances of shock and dehydration, pre-warmed (37°C) sterile isotonic normal saline solution (0.9% NSS) was injected (1 ml/mouse, *s.c.*). The same surgical procedure was followed for sham-operated (SO) mice, except ligation and puncturing of the cecum.

2.3 Grouping and Dosing of Animals

Animals were allotted in one of the following groups randomly- I: sham-operated mice (SO); II: sepsis mice (CLP); III: septic mice administered with IMI alone (CLP + IMI); IV: septic mice treated with t-AUCB alone (CLP+t-AUCB); V: septic mice treated with a combination of t-AUCB and IMI (CLP+t-AUCB+IMI). Sepsis was induced in all these groups (except SO) as described earlier. IMI was administered (@ 25 mg/kg b.wt,; *sc*) at 6 and 12 h post-CLP (Gr-III)[24,25]. While t-AUCB was administered (@ 0.1 mg/Kg, b.wt.; *i.p.*) at 6 and 12 h after induction of sepsis alone (Gr-IV) or in combination with IMI (Gr-V). The dose and dosage schedule for t-AUCB were selected on the basis of an earlier report[13].

2.4 Reagents and Chemicals

t-AUCB(4-[[trans-4-[[(tricyclo[3.3.1.1[3,7]]dec-1-ylamino) carbonyl] amino] cyclohexyl]oxy]-benzoic acid) was purchased from Cayman Chemical (Ann Arbor, Michigan, US) while phenylephrine hydrochloride (PE), acetylcholine chloride (ACh), and sodium nitroprusside dihydrate (SNP) were procured from Sigma (St. Louis, Mo, USA). Imipenem (IMI; Lupinem) from Lupin Ltd., India, was used. Stock solution and subsequent dilution of PE, ACh, and SNP were prepared using distilled water for the functional study. While t-AUCB stock solution was prepared using dimethyl sulfoxide (DMSO) and its subsequent dilutions were prepared freshly in sterile phosphate buffer saline (pH: 7.4) before administration to animals. IMI was reconstituted with 0.9 % sterile normal saline every day before use. The remaining chemicals used in the experiment belongs to analytical grade.

2.5 Tissue Collection and Isometric Tension Experiment

For isometric tension experiment, the same procedure was followed as described in our earlier publications[24,40]. Mice from different groups were euthanised by bleeding under xylazine-ketamine anaesthesia in the late phase of sepsis (18-19 h post-CLP). The abdomen and thorax were opened, and the thoracic aortic segment was then excised gently and immediately placed in cold (4°C) Modified Krebs–Henseleit solution (MKHS). Adherent surrounding tissue was then carefully separated to get clean vessels, and aortic rings (3-4 mm length) were made using a dissection stereo microscope (Motic, China). For tension protocol, prepared rings were quickly and carefully mounted on two 'L'-shaped hooks of stainless-steel and placed in a thermostatically controlled organ bath (Radnoti, USA) maintained at 37.0 ± 0.1 °C. The bath was filled with MKHS, which was continuously aerated using a medical gas containing 74% N_2, 21% O_2 and 5% CO_2. The rings were then equilibrated for 60 minutes under a resting passive tension of 1.0 g. After equilibration, tissue viability of the aortic rings was confirmed by exposing them to high potassium solution (80 mM) followed by several washings with prewarmed MKHS (37°C) to restore the resting tension. After a 20-minute stabilisation of the resting tension, cumulative concentration-dependent vaso-relaxant response to ACh (0.1 nM–3 µM) and SNP (0.01 nM–3 µM) were recorded in the aortic rings pre-contracted with phenylephrine (0.1-10 µM)[24,26]. The resultant tension changes were sensed by a highly sensitive isometric force transducer and recorded on a computer using the Lab Chart V7 Pro software (AD Instruments, Australia).

2.6 Effect of Sepsis and Treatment on Serum Biochemistry

For serum biochemical profile, blood samples were collected from different groups of mice via cardiac puncture (18-19 h post-CLP). The serum was separated by centrifuging the blood samples at 3000 rpm for 10 min and stored at −80 °C until further analysis. The alteration in the levels of renal (blood urea nitrogen; BUN and creatinine) and hepatic biomarkers (alanine aminotransferase; ALT and aspartate aminotransferase; AST) were estimated using a commercially available kit (Span diagnostics, Ltd., India).

2.7 Statistical Analysis

All the recorded experimental data are expressed as mean ± SEM, where 'n' denotes the number of arterial rings and 'N' indicates the number of animals used in the particular experimental protocol. Data were analysed using Prism software version 8.02 (San Diego, California, USA). The relaxant response to vasorelaxants was expressed as per cent maximal relaxation (R_{max}). The ceiling vaso-relaxant response (R_{max}) and EC_{50} (concentration required to produce 50% of the ceiling response) were computed following a nonlinear regression analysis method (sigmoidal dose-response curve with variable slope). The potency of a drug (pD_2) was calculated as $-\log EC_{50}$ value. Analysis of the concentration response curve was done by employing the two-way analysis of variance (ANOVA) followed by the Bonferroni *post-hoc* test. Differences in the biochemical parameters amongst the groups were compared using one-way ANOVA followed by Tukey's *post-hoc* test. Statistical significance was expressed at $p<0.05$, keeping a 95% level of confidence interval.

3. Results

3.1 Treatment with t-AUCB Improves Endothelial Function

Aortic rings from the SO group exhibited marked relaxant response to ACh (Figure 1a), indicating normal endothelial function (R_{max}: 86.47 ± 2.36 % and pD_2: 7.34 ± 0.07; n=10,

N=6) (Table 1). While in sepsis, a significant (p<0.05) drop in ACh relaxant response (R_{max}: 41.32 ± 4.68 %, n=10, N=6) (Figure 1b) without a change in pD_2 values (6.75 ± 0.15; n=10, N=6) was observed. Interestingly, septic mice treated with all the treatments significantly (p<0.05) improved ACh-mediated maximal vasorelaxation (Figures 1c-f), without a significant change in pD_2 values. The calculated maximal relaxation (R_{max}) and potency (pD_2) of ACh for the individual group are summarised in Table 1. Although an almost 20% improvement in ACh-mediated relaxation was noted following different treatments, overall relaxation was found to be less than the observed value in the SO group of mice.

To assess the effect of sepsis and different treatment protocols on endothelium-independent relaxation, vasorelaxing effects of the endothelium-independent nitrovasodilator, SNP, was studied in aortic rings isolated from various experimental groups. Figure 2(a-f) illustrates the tracing and concentration response curve of SNP (0.01 nM–3 µM) in the mouse aorta isolated from different groups. The observed pD_2 and R_{max} values for SNP in SO mice were 7.49 ± 0.16 and 100.46 ± 3.64 % (n = 12, N=6), respectively. SNP-mediated smooth muscle vasorelaxation remains unaltered in septic mouse aorta with pD_2 and R_{max} values of 7.11 ± 0.17 and 112.27 ± 3.34 % (n=9, N=6), respectively. Similarly, the relaxation response to SNP remained unaltered in septic mice treated with IMI alone (R_{max} 108.24 ± 3.56 % and pD_2 8.53 ± 0.10, n=11, N=6), t-AUCB alone (R_{max} 113.37 ± 4.59 % and pD_2 7.06 ± 0.12, n=9, N=4), or a combination of t-AUCB + IMI (R_{max} 118.19 ± 2.23 % and pD_2 7.51 ± 0.06, n=11, N=5) as compared to SO mice (Table 1). These results thus indicate that the responsiveness of aortic rings to SNP remained largely unaffected by sepsis and various treatment protocols.

3.2 t-AUCB Treatment Improves Hepato-Renal Function

Compromised multi-organ function and later on their failure, predominantly causes heavy mortality in septic patients and is positively correlated with the degree of endothelial dysfunction and sepsis outcomes. In comparison to the SO group, a significant (p<0.05) rise in levels of ALT, AST, BUN and creatinine level (Figure 3) in the CLP group was found, indicative of severe hepatic and renal damage. However, treatment of septic mice with either IMI or t-AUCB alone reduced the elevated levels of ALT, AST, and creatinine (Figures 3a-d). In this line, combined therapy with t-AUCB+IMI was found to be further effective in lowering the elevated levels of these biomarkers in septic mice (Figures 3a-d).

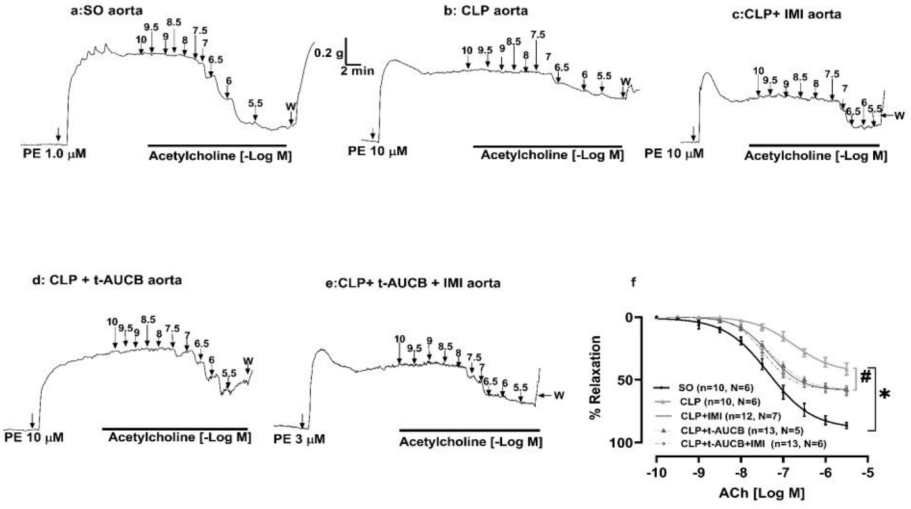


Figure 1. Fig 1 depicts effect of sepsis and treatments on endothelium-dependent relaxation to acetylcholine (ACh) in mouse aorta. Representative dose response curve indicates concentration-dependent relaxation to acetylcholine (ACh) (0.1 nM-3 µM) in the mouse aorta of SO **(a)**, CLP **(b)**, CLP+IMI **(c)**, CLP + t-AUCB **(d)**, and CLP + t-AUCB+ IMI **(e)** group. **(f)** illustrates the mean of concentration-response curves for the acetylcholine (ACh) in thoracic aorta obtained from different groups. 'n' and 'N' represent number of arterial rings and number of animals; while vertical bars denote SEM. Two-way ANOVA followed by Bonferroni *post-hoc* test was used for data analysis. *p< 0.05 vs SO. #p<0.05 vs CLP.

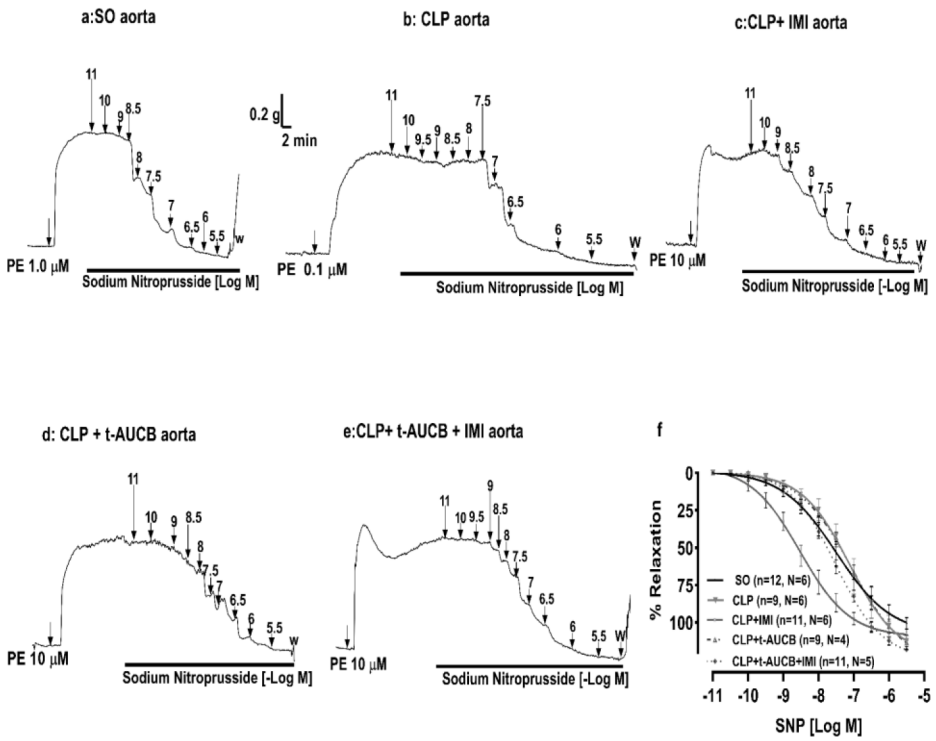


Figure 2. Effect of treatment on endothelium-independent relaxation to sodium nitroprusside (SNP) in aorta. Representative dose response curve indicates concentration-dependent relaxation to SNP (0.01 nM-3 μM) in mouse aorta obtained from SO **(a)**, CLP **(b)**, CLP+IMI **(c)**, CLP + t-AUCB **(d)**, and CLP + t-AUCB+ IMI **(e)** group. **(f)** illustrates the mean of concentration-response curves for SNP in thoracic aorta obtained from different groups. 'n' and 'N' represent number of arterial rings and number of animals; while vertical bars denote SEM. Two-way ANOVA followed by Bonferroni *post-hoc* test was used for data analysis.

Table 1. Effect of sepsis and different treatments on aortic vasorelaxation to Ach and SNP

Group	SO	CLP	CLP+IMI	CLP+t-AUCB	CLP+t-AUCB+IMI
pD_2 ACh	7.34 ± 0.07	6.75 ± 0.15	7.33 ± 0.07	7.29 ± 0.06	7.46 ± 0.05
R_{max} ACh (%)	86.47 ± 2.36	41.32 ± 4.68*	58.27 ± 3.45#	57.70 ± 3.02#	59.34 ± 3.31#
pD_2 SNP	7.49 ± 0.16	7.11 ± 0.17	8.53 ± 0.10	7.06 ± 0.12	7.51 ± 0.06
R_{max} SNP (%)	100.46 ± 3.64	112.27 ± 3.34	108.24 ± 3.56	113.37 ± 4.59	118.19 ± 2.23

Data are expressed as Mean ± SEM. Comparison of mean values of the groups was done using one-way ANOVA followed by Tukey's *post-hoc* test. *p< 0.05 *vs.* SO group. #p<0.05 *vs.* CLP group.

4. Discussion

Endothelial dysfunction majorly contributes to sepsis pathophysiology[5] and has a positive correlation with prognosis in septic patients[7,9,10]. Vasorelaxation to ACh, a marker for endothelial integrity, was significantly attenuated in the present study due to sepsis, which is in agreement with the earlier reported studies[24,26]. An acute rise in the levels of NO during inflammation, owing to the induction of inducible nitric oxide synthase expression (iNOS), accompanied by a drop in endothelial nitric oxide synthase (eNOS) mRNA expression, contributes predominantly to endothelial dysfunction during inflammation[24]. Endothelial dysfunction associated with multi-organ failure and mortality in sepsis requires a multimodal approach to speed up recovery and improve prognosis in septic patients. Targeted strategies aimed at restoring or preserving endothelial function using anti-inflammatory agents, antioxidants, and endothelial protective agents, along with control of bacterial population and mitigation of their toxins, were positively correlated with prognosis in septic patients[7,9,10]. IMI,

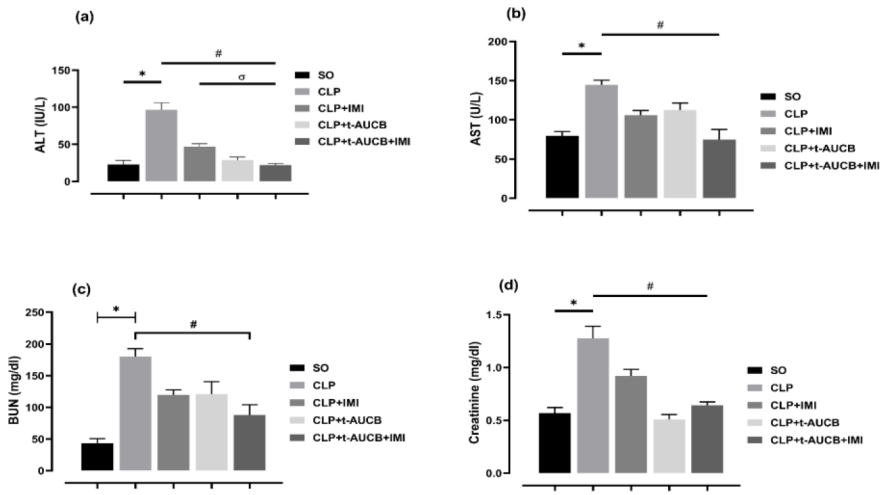


Figure 3. Bar diagrams showing the effect of sepsis and treatments on serum biochemical parameters- ALT **(a)**, AST **(b)**, BUN **(c)** and creatinine **(d)** in different groups of mice. Data values are expressed as mean ± SEM where vertical bars indicate SEM. Altered biomarkers levels were assessed using one-way ANOVA with Tukey's *post-hoc* test. $^{*}p<0.05$ vs. SO; $^{\#}p<0.05$ vs. CLP; $^{\sigma}p<0.05$ vs. CLP+IMI / CLP+t-AUCB (N=6 in each group).

an extended-spectrum carbapenem, is the antibiotic of choice for managing sepsis in hospital settings and for polymicrobial intraabdominal infections[27,28] and was found to be potent in reducing morbidity and mortality in the polymicrobial CLP model of sepsis in mice[29]. Administration of IMI alone improved the ACh relaxant response, along with a drop in elevated serum biochemical parameters, which further dropped down in mice receiving t-AUCB alone or in combination with IMI. Increased NO production via partial restoration of eNOS and reduced iNOS mRNA expression following IMI administration in sepsis could be responsible for improving endothelial response to ACh, as documented earlier[24]. t-AUCB, a potent and promising sEH inhibitor, has been found effective in restoring endothelial function in various inflammatory conditions like hypertension[12], endotoxemia[13], myocardial infarction[30], diabetes[31], etc. Treatment of septic mice with t-AUCB alone or with IMI improved the endothelium-dependent relaxation to ACh and liver and kidney parameters in the present study. In hypertension, t-AUCB treatment has been found to improve the ACh response in intrarenal arteries in rats[32] and also in the thoracic aorta in diet-induced metabolic syndrome in rats[34]. These actions of t-AUCB were mediated via restoration of eNOS mRNA and protein expression along with its phosphorylation[32]. Additionally, suppression of endothelial NF-κB signalling and reactive oxygen species (ROS) generation in these arteries has been found to contribute in restoring hypertension[32]. Moreover, inflammatory biomolecules generated via cyclooxygenase (COX) and lipoxygenase (LOX) pathways are the key driving players of inflammation. t-AUCB administration in endotoxemic mice has been reported to repress induction of iNOS and inflammatory mediators like 15-hydroxyeicosatetranoic acid (15-HETE), 5-hydroxyeicosatetranoic acid (5-HETE) and TXB_2 [33] and even of cyclooxygenase 2 (COX-2), 5-lipoxygenase (5-LOX), and thromboxane B_2 (TXB_2)[13]. The improved vasorelaxation to ACh and in the levels of liver and kidney biomarkers could be explained on the basis of t-AUCB effects on iNOS activity and other inflammatory mediators, besides the added role of IMI in controlling bacterial population and toxin release. Besides t-AUCB, other sEH inhibitors like AR9281 and AUDA were also found to be effective in restoring endothelial dysfunction in hypertension[16,35]. TPPU, another sEH inhibitor, regulated macrophage functions in terms of macrophage phagocytosis activity and caused a drop in inflammatory response in sepsis[21]. Similarly, statins, especially atorvastatin in combination with IMI, have also been found to improve ACh-mediated relaxation in septic mice[24].

Multiple organ failure contributes mainly to sepsis-associated deaths in hospitalised individuals, and vital organs like the liver, kidney, lungs, heart, etc., are the primary organs affected by sepsis[36,37]. An increase in serum levels of ALT, AST, BUN and creatinine implies severe hepatic and renal damage in sepsis. Multiple

organ dysfunction or failure can occur sequentially or simultaneously and is often linked to the modulation of other vital organ functions through mechanisms of organ crosstalk[38,39]. Significant elevation in these biomarkers in septic mice has also been reported previously[21,26,36]. Treatment of septic mice with IMI or t-AUCB alone reversed the elevated levels of ALT, AST, and creatinine; however, the combination of t-AUCB+IMI was further effective in reducing the elevated levels of these biomarkers. The observed beneficial effect of IMI in reducing hepatic and renal damage is in accordance with the previous finding in the CLP model of sepsis[42]. Action of IMI on inflammatory mediators and bacterial proliferation in sepsis was reported to improve survival time in septic patients[29,41] and thus is often recommended for the management of sepsis. Besides its anti-inflammatory role via repression of iNOS induction and production of other inflammatory biomolecules[13,33], t-AUCB were also found to prevent renal damage in diabetic mice by regulating elevated levels of blood glucose, BUN, creatinine, and protein[43]. Thus, t-AUCB+IMI together possibly produced synergistic action in septic mice in reducing bacterial proliferation, progression of the inflammatory cascade and inflammatory molecules, which may be attributed to the reduction of hepatic and renal biomarkers. In contrast to our findings, a drop in only AST but not ALT level was recorded following t-AUCB administration in rats with metabolic syndrome[34]. Moreover, improvement in liver and kidney function in septic mouse following prophylactic administration of N-[1-(1-oxopropyl)-4-piperidinyl]-N'-[4-(trifluoromethoxy)phenyl)-urea (TPPU) (sEH inhibitor) and 4-(5-phenyl-3-{3-[3-(4-trifluoromethyl-phenyl)-ureido]-propyl}S-pyrazol-1-yl) benzenesulfonamide (PTUPB) (dual COX-2 and sEH inhibitor), both in early and late phase of sepsis was also reported[20,21]. PTUPB administration has also been reported to dampen carbon tetrachloride (CCl_4) mediated liver fibrosis and the associated portal hypertension[18]. The improvement in serum biochemical profile following treatment could be due to improvement in ACh-mediated relaxation, owing to regulation of blood perfusion and may also be via t-AUCB action on limiting cytokine-mediated organ damage.

5. Conclusion

In conclusion, treatment with sEH inhibitor, i.e. t-AUCB, has a positive role in improving or restoring altered endothelial function in sepsis. Moreover, t-AUCB helped in reversing elevated levels of ALT, AST, BUN and creatinine. Although beneficial effects following sEH inhibition were found in the present study as reported in several other studies, further experimental studies assessing the impact of multiple doses of t-AUCB administration in improving sepsis outcomes, with its possible mechanism, are warranted. Nonetheless, sEH inhibition using t-AUCB is a promising target in various inflammatory conditions related to cardiovascular and other conditions.

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Author Contributions

RA: Conceptualisation, Methodology, Writing–original draft. DG.: Formal analysis, Investigation. BD: Assistance in investigation. HP.: Formal analysis, Investigation. AS and SC: Conceptualisation, Supervision, Review and Editing.

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