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REVIEW

Mechanistic insight on the role of leukotriene receptors in ischemic–reperfusion injury

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Abstract

Leukotrienes (LT) are a class of inflammatory mediators produced by the 5-lipoxygenase (5-LO) enzyme from arachidonic acid (AA). We discussed the various LT inhibitors and downstream pathway modulators, such as Mitogen-Activated Protein Kinases (MAPK), Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K/Akt), 5′-Adenosine Monophosphate-Activated Protein Kinase (AMPK), Protein Kinase C (PKC), Nitric Oxide (NO), Bradykinin, Early Growth Response-1 (Egr-1), Nuclear Factor-κB (NF-κB), and Tumor Necrosis Factor-Alpha (TNF-α), which in turn regulate various metabolic and physiological processes involving I/R injury. A systematic literature review of Bentham, Scopus, PubMed, Medline, and EMBASE (Elsevier) databases was carried out to understand the nature and mechanistic interventions of the leukotriene receptor modulations in ischemic injury. In the pathophysiology of I/R injuries, LT has been found to play an important role. I/R injury affects most of the vital organs and is characterized by inflammation, oxidative stress, cell death, and apoptosis leading to morbidity and mortality. sThis present review focuses on the various LT receptors, i.e., CysLT, LTC4, LTD4, and LTE4, involved in developing I/R injury in organs, such as the brain, spinal cord, heart, kidney, liver, and intestine.

Keywords Ischemic reperfusion injury · Leukotrienes · Leukotriene receptor · 5-Lipoxygenase

Abbreviations

5- LO/LOX	5-Lipoxygenase
AA	Arachidonic acid
AST	Aspartate aminotransferase
AMPK	5′-Adenosine monophosphate-activated protein kinase
ARF	Acute renal failure
ASM	Airway smooth muscle
BBB	Blood–brain barrier
BLT1	Leukotriene B4 receptors
Ca^{2+}	Calcium ion
cPLA2	Cytosolic phospholipase A2
CysLTs	Cysteinyl leukotrienes
ERK	Extracellular signal-related kinases
FLAP	5-Lipoxygenase activating protein
GPCR	G protein-coupled receptor
GPR 17	G protein-coupled receptor 17
GSH	Reduced glutathione
GTP	Guanosine -5′-triphosphate
HETEs	Hydroxyeicosotetraenoic acids
HPETE	Hydroperoxyeicosatetraenoic acid
I/R	Ischemic reperfusion
IRI	Ischemic reperfusion injury
JNK	Jun amino-terminal kinases
Kae	Kaempferide
LT	Leukotrienes
LTA4	Leukotriene A4
LTB4	Leukotriene B4
LTC4	Leukotriene C4
LTC4S	Leukotriene C4 synthase
LTD4	Leukotriene D4
LTE4	Leukotriene E4
LV	Left ventricular
LXA4	Lipoxin A4
MAPK	Mitogen-activated protein kinases
MCAO	Middle cerebral artery occlusion
MEK–ERK	Mitogen-activated protein kinase–extracellular signal-related kinase
MGST	Microsomal glutathione-S-transferase
MPO	Myeloperoxidase
NaB	Sodium butyrate
OGD	Oxygen–glucose deprivation
OPCs	Oligodendrocyte precursor cells

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PI3K	Phosphatidylinositol 3-Kinase
PKB	Protein kinase B
PLA2	Phospholipase A2
PMNL	Polymorphonuclear leukocytes
ROS	Reactive oxygen species
Sal A	Salvianolic acid A
TNF-α	Tumor necrosis factor-alpha
TXA2	Thromboxane A2
UDP	Uridine diphosphate

Introduction

I/R injury is a complex process that results in tissue injury. Researches have shown that replenishing ischemic tissues with blood flow cause persistent cellular injury or ischemic reperfusion (I/R) injury [1]. The clinical setting of I/R injury includes acute heart failure, gastrointestinal dysfunction, myocardial hibernation, systemic inflammatory response syndrome, cerebral dysfunction, and multiple organ dysfunction syndromes [2]. I/R injury affects most vital organs, such as the brain, heart, lungs, kidney, intestine, and liver. The risk factor associated with this disorder involves aging, stress, hyperlipidemia, hypertension, diabetes mellitus, metabolic syndrome, obesity, and hereditary factors [3]. The pathogenesis of I/R injury comprises various mechanisms, such as calcium overload, oxidative/nitrosative stress, and reactive oxygen species (ROS) [3]. ROS initiates lipid peroxidation in cell membranes, causing arachidonic acid to release prostaglandins (PGs) and leukotrienes (LT) [4]. The release of arachidonic acid stimulates the 5-lipoxygenase (5-LO) pathway, which produces LTs. Under physiological conditions, endothelial cells come into regular contact with circulating PMNL, known to have large amounts of LTA4 [5]. Endothelial cells' ability to metabolize LTA4 from activated polymorphonuclear leukocytes (PMNL) and modulate PMNL 5-LO activity could be essential for LT synthesis. The cerebral endothelium forms the BBB and limits many compounds in the brain through tight endothelial junctions, efflux transporters, and limited transcytosis. Endothelial receptor activation, in particular, increases vascular permeability and slows leukocyte rolling, facilitating leukocyte transmigration.

In contrast, non-endothelial receptors, which are typically found on resident/circulating leukocytes, facilitate leukocyte recruitment to the injury site and endothelial receptor activation [6]. Cerebral ischemia causes endothelial dysfunction, including increased transcytosis and a change to a pro-inflammatory phenotype to promote thrombus formation, emboli, and leukocyte adhesion and reduce blood flow. This review aims to summarize the involvement of LTs and their associated pathways in I/R injury for particular organs (cerebral, cardiac, renal, and hepatic).

Materials and methods

A systematic literature review of PubMed, Medline, Bentham, Scopus, and EMBASE (Elsevier) databases was carried out with the keywords "Ischemic reperfusion injury, Leukotrienes, Leukotriene receptor, Signalling pathway, 5-Lipoxygenase". The review was conducted using the above keywords to collect the latest articles and understand the nature of the extensive work done on leukotriene receptors in ischemic injury.

Physiology of leukotriene

The word "LT" is derived from "leukocytes," in which it is mainly produced, and "triene" refers to the presence of three conjugated double bonds that are a common structural feature of all LTs [7]. They are a group of inflammatory mediators that belong to a member of the eicosanoid family [8]. Arachidonic acid is affected by 5-LO and 5-LO-activating protein, which leads to the emergence of LT, the central proinflammatory lipid mediator. CysLTs belong to the LT family, because they share a cysteinyl group in their structure. CysLTs and leukotriene (LTC4, D4, and E4, respectively) produce effects by binding to sequenced G-protein-coupled receptors: a novel CysLTE receptor (GPR99), cysteinyl LT receptor 1 (CysLT1R), and cysteinyl LT receptor 2 (CysLT2R) [9]. LTC4 and LTD4 have the same affinity for CysLT2R, but LTD4 has a higher relationship for CysLT1R. LTE4 is the most stable ligand with a weak association for LTC4 and LTD4, although it has a more binding affinity for GPR99 [9, 10]. Montelukast is an LT antagonist that binds selectivity to the CysLT1R with high affinity, assisting in inhibiting any physiological actions of CysLTs such as LTC4, LTD4, and LTE4 at its receptor (BLT1, BLT2, CysLT1, and CysLT2) that may facilitate allergic reactions. All these ligands and receptors are discussed below, suggesting how its alleviating ischemic injury.

(a) Leukotriene biosynthesis

Various steps are involved in the formation of LT, such as the amount of phospholipid produced in the cell membrane by phospholipase A2 (PLA2) [11, 12], the accessibility of small molecules (like ATP), the intensity and catalytic activity of a protein's 5-LO pathways, and post-translation changes by 5-LO [13, 14]. The intracellular location of 5-LO is another variable that affects LT synthesis. Targeting this can likely contribute to discontinuation of the inflammatory process in an affected organ, i.e., brain, heart, liver, kidney,

and intestine (as discussed below). Calcium and ATP-dependent enzyme, 5-LO, catalyzes the first step in the production of LTs [15]. 5-LO then catalyzes molecular oxygen incorporation into AA into 5-hydroperoxy-eicosatetraenoic acid (5-HPETE) [16]. Cytosolic 5-LO translocates to the nuclear membrane when cells get activated. Before 5-LO can synthesize 5-HPETE from AA, a nuclear membrane protein called 5-LO activating protein is required. Compounds that block LT biosynthesis are now accessible through particular 5-LO inhibition, e.g., zileuton. There are also experimental drugs that can inhibit LT synthesis through 5-LO activating protein (FLAP) inhibition. The rate-limiting step in the LT origination is 5-HPETE rearrangement to establish the unstable LTA4 [15]. LTA4 is either hydrolyzed into Leukotriene B4 (LTB4) by enzyme LTA4 hydrolase or combines with reduced glutathione to form LTC4 by LTC4 synthase enzymes. LTC4 is subsequently transported from the cells to LTD4 and then metabolized into LTE4. LTC4, LTD4, and LTE4 are referred as CysLTs [17].

(b) LT receptors and their biological effects

There are four LT receptors, including two LTB4 receptor subclasses (BLT1 and BLT2), two CysLT receptor subclasses (CysLT1 and CysLT2), and one RBLT1 receptor [18]. Research indicates that CysLTs, especially LTC4, LTD4, and LTE4, are inflammatory lipid mediators produced from the arachidonic acid metabolism of the LO pathway [19]. Table 1 shows the receptor distribution and its binding affinity to the ligand along with its functions.

(c) LTB4/CysLTs

CysLTs are named after they were first discovered in leukocytes and had a chemical structure that includes cysteine and three conjugated double bonds. CysLTs mediate the effects of CysLTs [18] by acting on the surface of cell receptors [20], which are commonly known as CysLT1 and CysLT2. Mast cells, bronchial smooth muscle cells, macrophages, monocytes, and eosinophils are known to be activated by the CysLT receptors [21]. Coronary smooth muscle cells, adrenal medulla cells, cardiac Purkinje cells, and endothelial cells also express the receptor CysLT2 [22, 23]. As a result, antiLT therapy can be of benefit in different forms of psoriasis or urticaria, atopic dermatitis, and other skin disorders, such as Kawasaki, Sjogren Larsson disease, and bullous pemphigoid. AntiLTs may also help treat specific symptoms, such as pruritus, or may have an additive benefit when used in combination with other anti-inflammatory medications, such as antihistamines or corticosteroids. However, such use should ideally be done in controlled studies [24–26].

Table 1 List of various LT receptors and their ligand, along with their distribution and function in the body

Receptor	Ligand	Distribution	Function	References
BLT1	LTB4	Blood leukocytes and lymphocytes	Migration of vascular smooth muscles, activating NF-κB and inducing the subsequent production of inflammatory cytokines, bone homeostasis	[27–29, 32]
BLT2	LTB4	Blood leukocytes, lung, small intestine, liver, spleen, kidney, heart, ovary, thymus, muscle pancreas, colon, and placenta	Coordinating responses between cells or autocrine signals for modulating their parent cells' responses	[27, 30, 31, 33–35]
CysLT1	LTD4, LTE4	Peripheral blood leukocytes, ASM, Spleen and in interstitial lung macrophages	Airway bronchoconstriction and hyper-responsiveness to bronchoconstriction agents such as histamine; increased vascular permeability, edema, the influx of eosinophils and neutrophils, smooth muscle proliferation, collagen deposition, and fibrosis in various tissue sites; and mucus secretion by goblet cells, goblet cell metaplasia, and epithelial cell hypertrophy in the membranes of the respiratory system	[21, 22]
CysLT2	LTC4	Placenta, peripheral blood leukocytes adrenals, Heart, spleen	vascular permeability, inflammation, and tissue fibrosis without causing the constriction of bronchioles	[21–23]

The distribution of these LT receptors is such as: BLT1 in Blood leukocytes and lymphocytes; BLT2 in blood leukocytes, lung, small intestine, liver, spleen, kidney, heart, ovary, thymus, muscle pancreas, colon, and placenta; CysLT1 in peripheral blood leukocytes, ASM, spleen, and interstitial lung macrophages; CysLT1 in placenta, peripheral blood leukocytes adrenals, heart, spleen

Pathophysiology

The main mechanisms for reperfusion injury, which eventually contribute to edema or hemorrhagic transformation, result in severe neuronal death and neurological impairment. These include the impairment of the blood–brain barrier (BBB), oxidative stress, mitochondrial pathways, leukocyte invasions, platelet activations, and complement activation [36]. Oxidative stress plays a significant part in the pathogenesis of various clinical circumstances, including malignancy, diabetes mellitus, atherosclerosis, chronic inflammation, human immunodeficiency virus infection, and I/R injury [37]. There are multiple mechanisms for forming reactive oxygen species, particularly through xanthine oxidase as the prime source of development in certain systemic vascular organs [38]. As LTs are proven to be the active inflammatory lipid mediators, they perform a vital function in the pathogenesis of inflammation attributed to their characteristics [6], as shown in Fig. 1. LTs encourage the movement of almost all the types of leukocytes into the tissues and enhance the helper cells of type 2 T (tissue repair). The production and secretion of LT's present on resident and circulating cells are triggered by injury or proinflammatory stimuli, leading to edema in the affected tissue [26]. As a result, this feature exacerbates the inflammatory response and increases tissue damage. In the pathogenesis of inflammation, LT modifiers or receptor antagonists could be a possible target for managing inflammatory diseases, such as intestinal disorders, cardiovascular disorders, cerebral disorders, and so on [39]. In the pathophysiology of inflammatory disorders, LTs trigger events involving leukocyte activation, regulation of pro-inflammatory cytokines, and activation of various

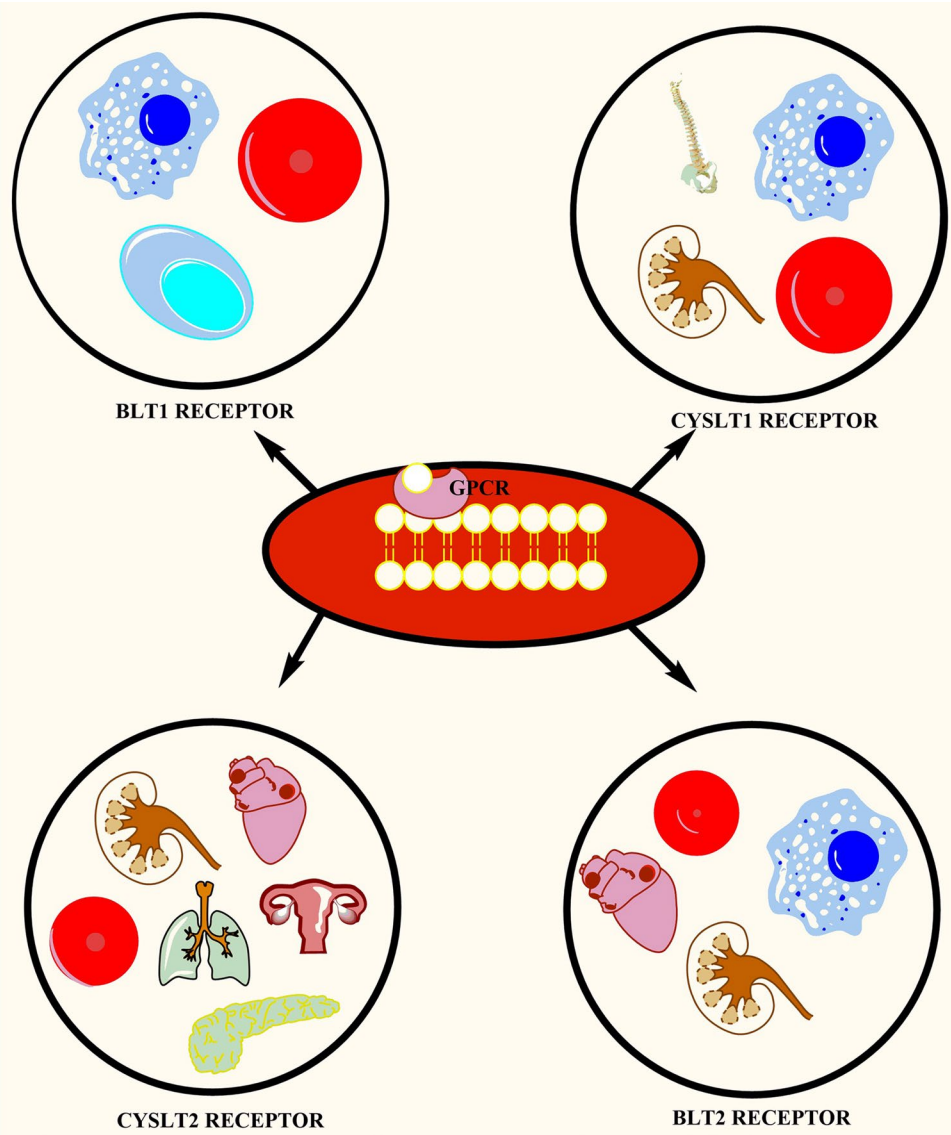

Fig. 1 Illustration of the expression of the LT receptor and its ligand in the body. The distribution of these LT receptors is such as: BLT1 in blood leukocytes and lymphocytes; BLT2 in blood leukocytes, lung, small intestine, liver, spleen, kidney, heart, ovary, thymus, muscle pancreas, colon, and placenta; CysLT1 in peripheral blood leukocytes, ASM, Spleen, and interstitial lung macrophages; CysLT1 in Placenta, peripheral blood leukocytes adrenals, heart, and spleen

downstream cascades that play a prominent role in neuroinflammation. Further studies are also needed, confirming the safety and efficacy of LT's inhibitors.

Downstream signalling pathways modulated by LTs (Fig. 2)

LTs modulate various downstream signalling pathways, such as PI3K (Phosphatidylinositol 3-Kinase), MAPK, AMPK (5′-Adenosine Monophosphate-Activated Protein Kinase), TNF-α (Tumour Necrosis Factor), NO (Nitric Oxide), PKC (Protein Kinase C), Bradykinin, NF-κB (Nuclear Factor-κB), and Egr-1 (Early Growth Response), as depicted in Fig. 2.

i. PI3K/Akt pathway

The PI3K/Akt pathway is a highly essential intracellular signaling pathway in the cell cycle process. It also has to do with cell proliferation, survival, and apoptosis. Regulation of PI3K activation phosphorylates and activates Akt, which then moves to the cell membrane [40]. Through stimulation of the receptor LTD4, specific downstream signaling pathways are triggered. LTD4 further promotes the ruffle of the cell membrane by a signaling PI3K that results in the activation of protein kinase Akt/protein kinase B (PKB) and the tiny Guanosine-5′-triphosphatases (GTP), Rho, and Rac [41]. Various studies have demonstrated the PI3K/Akt signaling system's involvement in myocardial I/R injury in diabetic rats. Salvianolic acid A (Sal A), a novel PI3K/Akt inhibitor, exerts anti-apoptotic action in myocardial I/R injury and improves cardiac functional recovery after PI3K/Akt reperfusion signaling through stimulation of LTD4 [42]. Sodium butyrate (NaB) has also been shown to reduce cerebral I/R damage by reducing inflammatory and oxidative stress and lowering in vivo apoptosis. In addition, NaB investigated its antiapoptotic properties in cerebral I/R injury via the LTD4-activated PI3K/Akt signaling pathway and demonstrated a therapeutic opportunity for stroke in clinical studies. (Table 2) [43]. Kaempferide (Kae) treatment in myocardial I/R injury contributes to the recovery of cardiac function by lowering myocardial infarction size, anti-inflammatory effects, apoptosis of cardiac myocyte, and oxidative stress. Alternatively, stimulation of the PI3K/Akt pathway

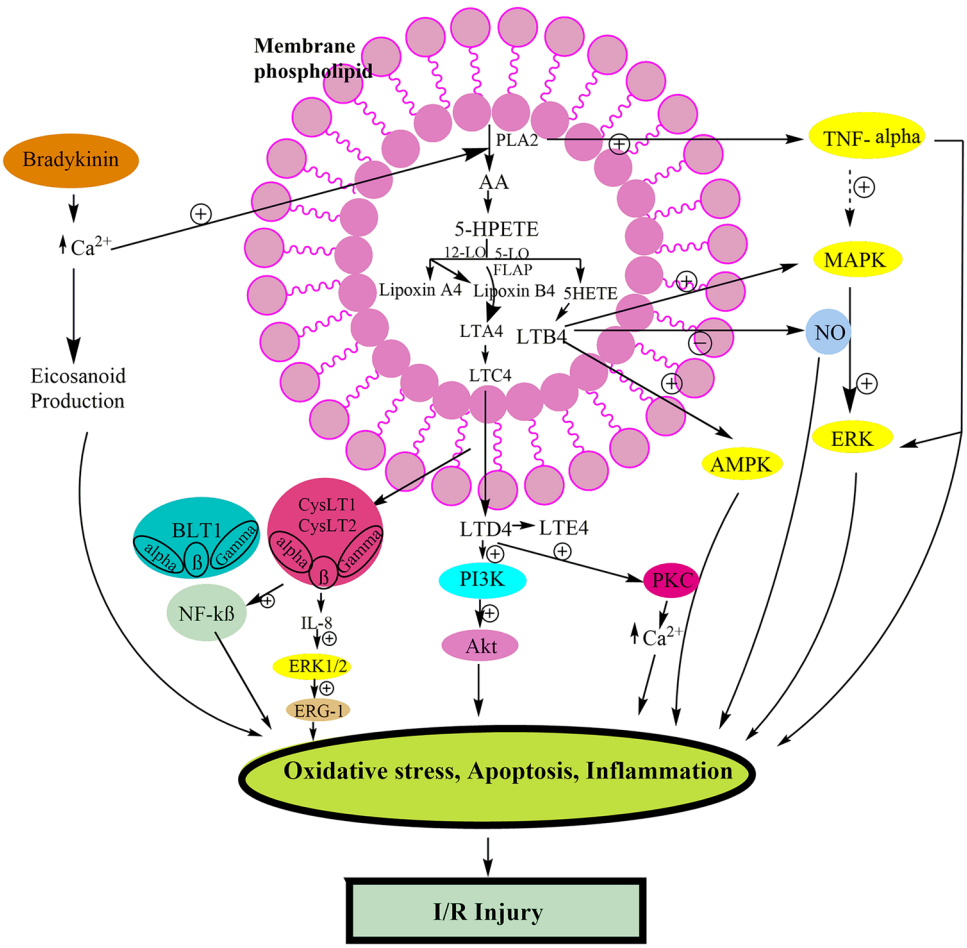

Fig. 2 Schematic diagram that depicts the synthesis of diverse LTs with the help of membrane phospholipids and the different downstream signaling pathways mediated by LTs, such as MAPK, PI3K/Akt, AMPK, TNF-α, Bradykinin, NO, PI3K, PKC, EGR-1, and NF-KB which further contributes to inflammation and apoptosis and ultimately leads to I/R injury

Table 2 List of LT inhibitor and their mechanism of action concerning the particular organ, where they modulate I/R injury

Name of LT inhibitor	Particular organ where LT modulate its action	Mechanism of action	References
NaB	Cerebral	Acts via reducing inflammatory and oxidative stress along with lowering the in vivo apoptosis	[43]
Kae	Cerebral	Acts by lowering myocardial infarction size, anti-inflammatory effects, apoptosis of cardiac myocyte, and oxidative stress	[44]
Montelukast	Cerebral	Shows its action by promoting fiber connectivity up to 8 weeks after middle cerebral artery occlusion (MCAo), using different experimental approaches	[83]
Zafirlukast	Cerebral	Act substantial decrease in lipid peroxidation, serum nitrite, lactate dehydrogenase, and cerebral infarction	[84]
LXA4	Cerebral	Act by preventing the upregulation of both LTB4 and LTC4 along with anti-apoptotic and pro-resolution properties	[85]
Caffeic acid	Cerebral	It exerts its effects by acting as an anti-apoptotic, anti-inflammatory, and anti-oxidative agent	[79]
Pranlukast	Cerebral	Pranlukast attenuate the lesion volume, increase the neuron density and inhibit the ischemia-induced glial car formation, and finally improving the neurological deficits and the motor-sensory recovery	[87]
Montelukast	Intestine	Acts by decreasing the production and release of IL-6 in the small intestine	[100, 101]
Montelukast	Hepatic	Montelukast decreases I/R-induced oxidative injury and hepatic dysfunction, thus, attenuates hepatic I/R injury	[106]
Zafirlukast	Renal	It shows its effect through anti-inflammatory action, decreased infiltration of neutrophils into renal tissues, and oxidative stress following attenuation of P-selectin expression	[113]
Montelukast	Renal	Montelukast protects the kidney tissue by suppressing the infiltration of neutrophils, balancing the oxidant–antioxidant status, and controlling the production of inflammatory mediators	[115]
ACF-(OPDChaWR)	Renal	It exerts its effect through inhibiting or preventing I/R-induced hematuria, vascular leakage, tumor necrosis factor-alpha (TNF-α) and myeloperoxidase (MPO) tissue levels, and aspartate (AST) and creatinine serum levels	[119]

through LTD4 may serve a vital role in the protective effects of Kae treatment [44]. Thus, this particular pathway's crucial role, i.e., PI3K/Akt, is elucidated in regulating diverse cellular functions and playing a therapeutic target in managing various diseases.

ii. MAPK pathway

Four different kinases share a similar sequence with the MAPK signaling pathway components: ERK1/2, Jun amino-terminal kinases (JNK1/2/3), p38, and ERK5. Cell proliferation, differentiation, migration, senescence, and apoptosis are documented to be associated with MAPK/ERK pathway [45]. ERKs are known to activate many transcription factors, such as ELK1 and some downstream protein kinases [46]. This process is regulated by growth factors, stimulation of glutamate receptors, increase of Ca2 + levels intracellular and oxidative stress, factors that are activated by I/R injury [47, 48]. MAPK chiefly serves as a facilitator of cell stresses, including inflammation and apoptosis [49]. Phosphorylation of cytosolic phospholipase A2 (cPLA2) is a critical step in activating the MAPK family, including p38 kinases, ERK1/2. Several studies have explained PLA2′s prominent role in several inflammatory conditions. In addition, they have confirmed that cPLA2 plays a central role as a mediator and inflammatory regulator in the synthesis of eicosanoids [50]. ERK or cPLA2 inhibition selectively blocks the development of LTs B4-induced ROS [51]. Moreover, several studies suggest that the MEK1–ERK1/2 branch of the MAPK pathway, which acts by directly inhibiting myocyte apoptosis and thus in cardiac I/R injury, is cardio-protective [52]. Consequently, the MAPK pathway is related to inflammation progression, and the attenuation of that pathway leads to I/R injury management.

iii. AMPK pathway

In terms of AMPK, It is an evolutionarily conserved serine/threonine kinase that was first identified as a critical regulator of cellular energy homeostasis. AMPK regulates various metabolic and physiological processes, and its activity is disrupted in chronic diseases, such as inflammation [53]. Suppressing the LTB4/BLT1 signaling pathway via AMPK activation has been shown in studies to be a potential therapeutic approach for septic cardiac dysfunction. It may prevent cardiac apoptosis caused by inflammatory inhibi-

tion of mitochondrial dysfunction. Activation of the LTB4/BLT pathways by 5-LO (a critical enzyme for LTB4 synthesis) via AMPK activation may result in atherosclerotic plaque instability [54].

Consequently, selective inhibition of BLT1 could be a successful strategy to avoid damage to the myocardial I/R injury. The AMPK signaling pathway has been triggered by various factors, including adiponectin, omentin, and mitochondrial dehydrogenase, which contribute to cardiac I/R injury protection via LT receptor inhibition [55]. Due to its role as a central regulator, AMPK is considered a potential therapeutic target for treating various diseases associated with I/R injuries.

iv. NF-κB pathway

NF-κB is a family of inducible transcription factors that regulates a vast spectrum of genes engaged in multiple immune and inflammatory response processes [56]. NF-κB also plays a significant role in controlling the survival, activation, and differentiation of innate immune cells and inflammatory T cells [57]. Research indicates that CysLT2R might stimulate the M1 polarization of microglia by triggering the NF-κB signaling pathway and facilitating neuronal death and inflammation. Using CysLT2R inhibition to treat cerebral ischemic stroke caused by the NF-B signaling pathway could be a promising therapeutic approach [58–60]. 5-LOX inhibitors such as (N-[3-(-fluorophenoxy) phenyl]-1-methyl-2-propenyl]-N-hydroxyurea (BW-B 70C) were reported to have therapeutic potential for treating neuroinflammation in ischemic stroke injury [61]. LPS has been documented to downregulate the secretion of CysLT and the expression of LTC4S genes in mononuclear phagocytes through an NF-κB-mediated mechanism [62]. This validates the pathway's inflammation status, resulting in IR injury.

v. Egr-1 pathway

Activation of extracellular signal-regulated protein kinase-1 and kinase-2 (ERK1/2) suppresses inflammation by upregulating Egr-1 (a transcription factor) [63–65]. It controls the activity of inflammation, differentiation, growth, and development-related target genes [66]. CysLTs (LTD4 and LTC4) are known to stimulate the expression and release of pro-inflammatory cytokine IL-8 by triggering the CysLT2 receptor regulated by the ERK1/2–Egr-1 pathway. The ERK1/2–Egr-1 pathway will explain the function of the CysLT2 receptors in the development of inflammation and pharmacological management. The impacts of this signal pathway have yet to be described [65]. Hence, given its extensive regulation mode, the Egr1 functions are complicated and promote inflammation and I/R injury.

vi. TNF-α pathway

TNF-α was first identified as a circulating factor that regulates the inflammatory response. TNF is associated with two separate receptors, called TNFR1 and TNFR2, expressed differently on cells and tissues and activate distinct and overlapping pathways for signal transduction. Such multiple signaling cascades result in several cellular responses, including regeneration, cell death, differentiation, migration, and proliferation [67]. Group IVA, cPLA2α, which cleaves arachidonic acid preferentially from phospholipids, plays a factor in tissue damage and apoptosis. Downstream signals include cPLA2α activation in response to TNF-α, a mediator of I/R injury. Researchers suggest that the endogenous TNF-α signaling could be an upstream cPLA2 activation regulator during hypoxia–reoxygenation (H/R) and that cPLA2 activation acts in conjunction with TNF-α signaling in H/R injury [68]. Earlier, it was shown that TNF-α were sometimes involved in multiple signaling pathways resulting in cPLA2α activation, and it may include both TNFR-1 and TNFR-2 in a way that is either independent of p38 MAPK and ERK1/2 [69]. Disruption of cPLA2 slightly attenuated myocardial I/R damage by inhibition of TNF-α-mediated pathways [68]. TNF-α has been shown to play a significant role in I/R injury with the ever-expanding knowledge of TNF and its signaling pathways.

vii. NO pathway

Nitric oxide (NO) is a signaling molecule that plays a significant role in inflammatory pathogenesis. It works against inflammation under normal physiological conditions [70]. Prior studies have shown that certain factors, namely, nitric oxide, LTs, platelet-activating factor (PAF), and adhesion molecules, were involved in lipid peroxidation or neutrophil aggregation associated with reperfusion-induced injury [71]. On the other hand, exogenous NO was also shown to have a protective impact on the I/R damage [72]. Studies have recorded that NO synthase inhibitor pre-treatment decreases ischemia–reperfusion injury in the rabbit's skeletal muscle, isolated rabbit heart, and rat cerebrum [73]. Arndt et al. have noted that the enhanced adherence and emigration of leukocytes associated with NO synthesis inhibition involves the potent inflammatory agents PAF and LTB4. It has been confirmed that PAF and LTB4 aid in mediating the worsening of I/R caused by NO inhibition [74]. Finally, the undesired effects have proven to be a part of inflammation and its related I/R injury [72].

viii. Bradykinin pathway

Bradykinin is a low-molecular-weight peptide that engages in inflammatory processes due to its

potential to promote endothelial cells, resulting in nitric oxide production [75]. Inflammatory reactions are triggered during I/R injury, followed by the production of inflammatory cytokines, such as TNF-α, interleukin (IL)-1, and arachidonic acid metabolites, including TXA2, and PGI2, PGE2, and LT [76]. The rise in intracellular or extracellular calcium induced by the inflammatory mediator bradykinin activates PLA2 [77]. Bradykinin causes eicosanoid development through PLA2 activation, and it was found that FR173657 (FR), a bradykinin B2 receptor inhibitor, can decrease eicosanoid development pulmonary I/R injury [78]. Therefore, bradykinin caused inflammation via bradykinin pathways, and its inhibitors attenuated the progression of I/R damage.

A schematic diagram depicting the synthesis of various LTs using membrane phospholipids and different downstream signalling pathways mediated by LTs. LTC4 (produces within the phospholipid membrane), LTD4, and LTE4 (produces outside the membrane) activate CysLTs present in the body, further activating IL-8, NF-κB signaling pathways, and leads to the progression of I/R injury. LTD4 also causes inflammation by activating PI3K and the PKC signaling pathway. PLA2 causes the activation of TNF-α, which contributes the inflammation and I/R damage directly/indirectly by activating MAPK and ERK. PLA2 also links with the bradykinin pathway and gets activated through the increase in Ca^{2+} level. This increase in Ca^{2+} level produces eicosanoids and, hence, causes I/R injury via inflammation. LTB4 stimulates AMPK and MAPK and attenuates NO, which gives rise to inflammation and ultimately causes I/R injury.

Role of LT inhibitors in different I/R injury studies

Ischemic stroke is a worldwide leading factor of death and disability. Ischemic stroke develops from temporary or permanent cerebral blood flow reduction, resulting in a functional and structural damage in different brain regions [79]. A growing array of data indicates that inflammation and oxidative stress are involved in stroke pathology [80].

(i) LT in cerebral I/R injury

Cerebral ischemia causes inflammation within the infarction in response to necrotic cells. Consequently, necrotic cells cause inflammatory cells to produce ROS and inflammatory cytokines [81]. Inhibitors of LT synthesis limit the damage after transient cerebral ischemia in gerbils, which first raised the idea of LT production in the ischemic brain (Table 2) [82]. As previously stated, CysLTs are potent pro-inflammatory and immune-modulating lipid mediators involved in inflammatory diseases, and their function in the human brain has been improved following an acute cerebral ischemia process. Antagonism of the CysLTs receptor can protect against ischemic damage. A study concluded that Montelukast, a CysLT1R antagonist, improved fiber re-organization and long-term functional recovery after brain ischemia, augmenting recruitment and maturation of OPCs (oligodendrocyte precursor cells). [83]. Zafirlukast, a CysLT antagonist, has a dose-dependent neuroprotective activity with significant declines in lipid peroxidation, serum nitrite, lactate dehydrogenase, and cerebral infarction. This suggests the role of zafirlukast in cerebral I/R injury worldwide [84]. Changes in signal transduction pathways involving cell survival and death are correlated with I/R injury. Lipoxin A4 (LXA4), a biologically active eicosanoid with anti-inflammatory and pro-resolution properties, has neuroprotective effects in brain ischemia. LXA4 has been reported to prevent upregulation by OGD (oxygen–glucose deprivation) or MCAO (middle cerebral artery occlusion) of both LTB4 and LTC4 and extracellular signal-regulated kinase (ERK) phosphorylation [85]. LTs are key inflammatory lipid mediators, and 5-LO catalyzes the first step in AA biosynthesis of LTs, focused on the several active pathophysiological actions of LTs. The 5-LO pharmacological intervention is well known in therapeutic development [86]. In animal models of cerebral ischemia, 5-LO inhibitors such as caffeic acid have been shown to prevent the brain against ischemic damage. They exhibit anti-apoptotic, anti-oxidative, and anti-inflammatory properties [79]. Pranlukast, a CysLT-1 antagonist, inhibited acute, subacute, and chronic ischemic injury after focal cerebral ischemia [87]. The post-ischemic treatment of pranlukast had a long-term protective effect on MCAO mice like reduced lesion volume, increased neuronal density, inhibited glial scar formation from ischemia, and ultimately improved neurological and motor-sensory recovery [88]. G-protein-coupled receptor 17 (GPR 17), a previously orphaned receptor, is now known to connect nucleotides and CysLTs in ischemic/inflammatory responses [89–91]. More analysis proves that GPR17 is also engaged in a wide variety of pathological processes, such as cerebral, myocardial [92, 93] ischemic injury, and damage to the spinal cord [94–97]

(ii) LT in intestine I/R injury

Intestinal ischemia–reperfusion (I/R) is a commonly emerging condition that brings high morbidity and mortality during small bowel transplantation, abdominal and thoracic vascular surgery, hemorrhagic shock, and procedure using cardiopulmonary bypass. Reperfusion of chemically compromised intestinal tissue also worsens

tissue damage. It is known to be an effector of local and distant inflammation and multiple organ failure, which is still the leading cause of death in critically ill patients [98]. LTB4 encourages chemotaxis of leukocytes and adhesion to post-capillary venules endothelium. The CysLTs, LTC4, LTD4, and LTE4 evoke macromolecular leakage from the section of the vessel. Both endothelial leukocyte adhesion and postcapillary macromolecular leakage distinguish microcirculatory failure after ischemic reperfusion, implying LT's role as mediators in ischemic–reperfusion injury [99]. Montelukast is a selective, reversible CysLT type 1 receptor antagonist reported for its anti-inflammatory activity in clinical practice. It was believed to immediately safeguard the liver and kidneys after intestinal IRI by decreasing the production and release of IL-6 in the small intestine. Likewise, Montelukast may inhibit CysLT1R expression in the liver and kidney. It has been shown to limit intestinal mucosal injury and apoptosis following intestinal IRI and damage the liver and kidneys (Table 2) [100]. Following intestinal I/R injury, the effect of Montelukast on colon anastomosis was studied, and observed that Montelukast could reduce the adverse impact of I/R on intestinal anastomosis [101].

(iii) LT in hepatic I/R injury

For certain surgical cases, including liver transplantation, liver resection, and trauma, I/R liver damage is a significant complication [102]. Active lipid mediators that improve vascular permeability and neutrophil recruitment are the CysLTs (cLT; LTC(4), LTD(4), and LTE(4) and LTB(4) LTs, typical features of hepatic (I/R) injuries. Several laboratory research has shown that cLT production in the liver is increased after hepatic I/R and hepatic edema and liver dysfunction. CysLTs may lead to the inflammatory phase condition and exert hepatotoxicity. In comparison, after hepatic I/R, LTB4 appears to be liable for neither liver nor lung injury [103]. Several researchers examined that the hepatic I/R injury up-regulated the LTC4S mRNA and protein expressions in hepatocytes, sinusoidal endothelial cells and improved the synthesis enzyme activity of LTC4s. It indicates that LTC4 accumulation after hepatic I/R can be partially induced by up-regulation of the expression LTC4S [104]. Recruited macrophages serve a crucial role in liver repair following an acute injury to the liver. LTB4 is a powerful macrophage chemo-attractant. Different studies explored the function of LTB4 receptor type 1 (BLT1) in liver repair throughout hepatic I/R injury.

Furthermore, it has been reported that BLT1 signaling serves as a liver repair factor after hepatic I/R by enhancing EGF expression in recruited macrophages. The development of a specific BLT1 agonist may help liver recovery from acute liver injury [105]. Some studies indicate that montelukast, a CysLT1 receptor antagonist, decreases I/R-induced oxidative stress and hepatic dysfunction, suggesting that CysLTs are among the significant mediators to tissue damage following I/R in the hepatic system. Montelukast, including its effectiveness as an anti-inflammatory and antioxidant, appears likely to justify consideration as possible therapeutic agents in hepatic I/R [106].

(iv) LT in cardiac I/R injury

The main factor in the morbidity and mortality associated with coronary artery disease is myocardial I/R. Three levels of I/R-induced cardiac injury were established depending on the ischemia's extent [107]. CysLTs cause endothelial inflammation and proliferation through CysLT2R/Rho kinase and CysLT1R/ERK-based pathways that serve a crucial role in cardiovascular disease etiology atherosclerosis and myocardial infarction [108]. Based on a study, endothelium-targeted overexpression of CysLT2R worsen myocardial I/R injury and exacerbates inflammatory gene expression, leading to accelerated left ventricular (LV) remodeling and the development of cardiac impairment [109]. Experiments showed that myocardial ischemia increased the growth of left ventricular hypertrophy, LT, and causes the translocation of 5-LO (LOX) [110]. As a result, LTs can lower inflammatory mediators and worsen ischemic injury [111].

(v) LT in renal I/R injury

A significant health issue with high mortality and morbidity is an acute renal failure (ARF). I/R is one of the major causes of acute renal failure. The key factors triggering I/R are estimated to be an inflammatory process and oxidative stress. I/R injury pathogenesis is considered to include cytokines and mainly surface adhesion molecules, the expression of which initiates the attachment of inflammatory cells. Renal IRI production is influenced by renal inflammation, and renal I/R damage improves slowly after reperfusion. CysLTs was active in many of the inflammatory conditions. Renal I/R injury is an invariable outcome of renal transplantation, which is a clinically significant issue. The study reveals that MK-886 substantially reduced kidney damage by counteracting inflammatory and oxidative processes resulting from I/R [112]. The researcher highlight that zafirlukast, a CysLT receptor blocker, decreases the frequency of ischemic acute renal failure, infiltration of neutrophils into renal tissues, and oxidative stress following attenuation of P-selectin expression (Table 2) [113]. A potent lipid mediator in allergic disease, the CysLT1, works through the CysLT1R receptor, shown to be expressed in rat renal I/R injury. The highest renal I/R injury has been reported several hours after the highest CysLT1R expression. These findings indicate that CysLT1R may play a significant role in kidney I/R injury [114]. Oxygen-free radicals are essential components of the processes found during I/R.

Montelukast receptor antagonist (CysLT1) reversed oxidant reactions caused by I/R, enhanced microscopic damage, and renal function. Montelukast protected the kidney tissue by suppressing neutrophils' infiltration, balancing the oxidant–antioxidant status, and controlling the production of inflammatory mediators [115]. As a chemo-attractant and chemo-activator, LTB4 can indirectly induce renal injury, concluding that LTB4 can stimulate neutrophils to produce TxA2, OFR, and lysosomal enzymes. Therefore, some research proves that inflammatory mediators regulate post-ischemic renal injury [116] and clearly show that LTB4 is one of the primary mediators of neutrophil aggregation and renal dysfunction in rats [117]. The C5a receptor is a member of the broad class of seven G-protein-linked transmembrane receptors. C5a receptors are focused on blood granulocytes (neutrophils, eosinophils, and basophils and inflammatory tissue cells (macrophages, mast cells, and microglia) [118]. C5a has been involved in various pathophysiological disorders, including kidney damage caused by ischemia/reperfusion. As a novel and unique C5a receptor antagonist, the cyclic compound AcF-(OPdChaWR) reduced I/R-induced renal injury in rats by inhibiting or preventing I/R-induced hematuria, vascular leakage TNF-α and MPO tissue levels, and AST and creatinine serum levels [119].

(vi) LT in spinal cord I/R injury

Paraplegia from spinal cord injury is a debilitating and undesirable complication of thoracoabdominal aortic surgery, varying from 2.9% to 38% [120]. Various aortic cross-clamping, the thoracic or thoracoabdominal aortic aneurysm surgery, can provoke spinal cord ischemia and lead to severe postoperative complications. Spinal cord protection from I/R injury requires multimodal management (Fig. 3). Previous studies have suggested macrophage, and neutrophil releases of oxygen-free radicals are correlated with I/R injury (IRI). Free radical production, lipid peroxidation, or calcium influx into cells can cause neuronal cell death in the spinal cord [121]. A researcher also demonstrates that the use of iloprost (a stable prostacyclin–montelukast) combination in the rat model of spinal cord prophylactic use may minimize ischemic damage through anti-inflammatory effects that may provide more substantial neurological results [122]. Montelukast has also been shown to enhance motor recovery and lessen IL-6 levels in the I/R injury spinal cord. Montelukast's protective effects could be due to its antioxidative, anti-inflammatory, and neuroprotective action potential.

Clinical trials

In relevance with human health and disease, LT has been intensely investigated, and it continues to be of considerable clinical interest. The following table explains the clinical trials done to date (Table 3).

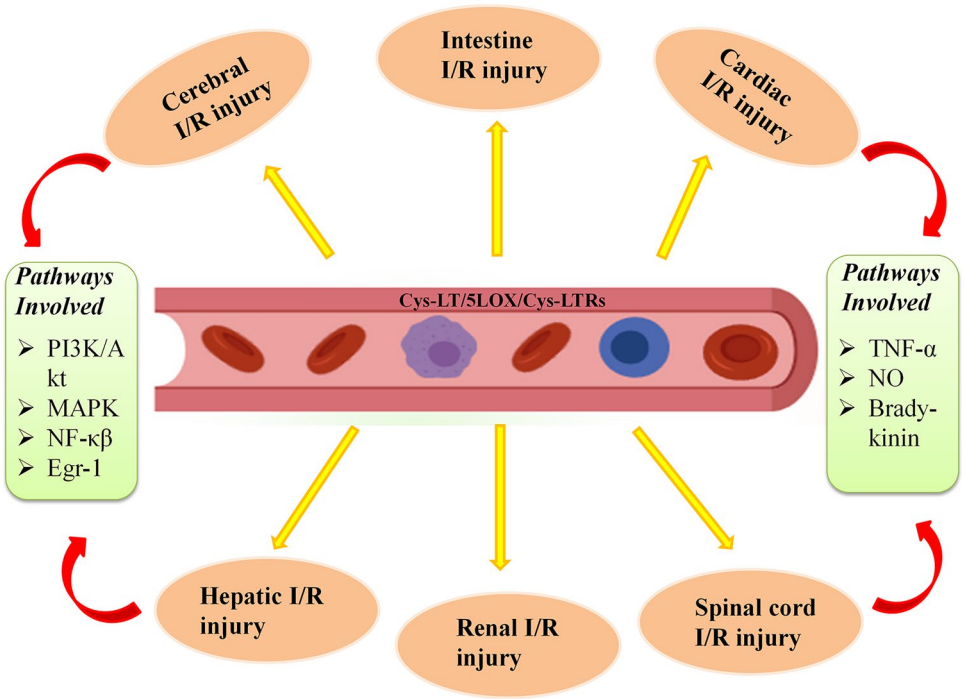

Fig. 3 Schematic diagram showing the involvement LT's via several pathways in various I/R injury

Table 3 Depiction of various LT modulators in clinical trials for ischemic injury

S. no.	Drug	Phase	Condition	NCT number
1	Montelukast	Phase 3	Acute lower limb ischemia	NCT04277702
2	AZD5718	Phase 2	Myocardial Ischemia	NCT03317002
3	Montelukast	Completed	Myocardial Ischemia	NCT00379808
4	AZD5718, oral suspension	Completed	Myocardial Ischemia	NCT03400488
5	VIA-2291	Phase 2	Myocardial Ischemia	NCT00358826
6	AZD5718 tablets	Phase 1	Myocardial Ischemia	NCT03420092

Conclusion

The pathology of ischemic reperfusion injury is better understood, and new therapeutic approaches are being researched. In the above scientific discussion, it has been shown that LTs elevate the levels of Ca^{2+} and ROS, which collectively contribute to ischemic tissue injury. Lipid mediators, such as cLT, LTC4, LTD4, and LTE4, and LTB4, facilitate vascular permeability and the recruitment of neutrophils, which is associated with IR. Besides, endothelial cell and leukocyte interactions lead to persistent epithelial cell hypoxia, inflammation, and dysfunction. Various therapeutic targets to prevent or restrict ongoing injury have been discussed in the review. New research has indicated that LTs play a significant role in the pathology of the inflammatory condition, especially regarding inflammation triggered by leukocytes and high levels of LTB4. Different drugs have been discussed that suppress their biosynthesis or antagonize their actions as critical therapeutic developments in inflammatory disease management. The review describes the downstream signaling pathways, which are modulated by LTs. The LT pathway's role as a promising new approach to limit I/R-induced tissue damage for different types of cerebral, cardiac, renal, and hepatic I/R injury has been explored.

Future perspectives

The field of research into LO and LT has progressed significantly in recent years and has reached a high development level. Nonetheless, as is often the case with physiologically related research areas, the field of LOs and LTs continues to produce exciting discoveries and novel pathways for discovery. Given scientific data on all the main proteins, i.e., cPLA2α, 5-LO, FLAP, LTA4 hydrolase, and LTC4 synthase, it is still unclear how they physically and functionally assemble and interact. The research will likely reveal new opportunities for interfering with the biosynthesis of LT. New LT4 receptors have recently been discovered, and their functions in CysLT signaling and associated diseases such as asthma need to be explained [123]. Recently, the structure of receptors such as the β2-adrenergic receptor has been resolved, indicating that the structure of BLT and CysLT receptors will be determined [124]. The pharmaceutical industry, in comparison, has lagged far behind in developing specific CysLT2R antagonists [125]. Blocking CysLT2R activation during reperfusion after myocardial, cerebral, renal, and hepatic infarction may be an effective adjuvant to thrombolytic therapies and percutaneous intervention to reduce their damage [109].

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Declarations

Conflicts of interest There are no conflicts of interest.

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