Review

From Hypertension to Beyond: Unraveling the Diverse Mechanisms of Olmesartan in Disease Modulation

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ABSTRACT

Olmesartan, originally known for its antihypertensive properties, exhibits promising potential in addressing inflammation-mediated diseases. As an angiotensin II receptor blocker (ARB), Olmesartan influences pivotal pathways, including reactive oxygen species, cytokines, NF-κB, TNF-α, and MAPK. This suggests a viable opportunity for repurposing the drug in conditions such as ulcerative colitis, neuropathy, nephropathy, and cancer, as supported by multiple preclinical studies. Ongoing clinical trials, particularly in cardiomyopathy and nephropathy, suggest a broader therapeutic scope for Olmesartan. Repurposing efforts would entail comprehensive investigations using disease-specific preclinical models and dedicated clinical studies. The drug's established safety profile, wide availability, and well-understood ARB mechanism of action offer distinct advantages that could facilitate a streamlined repurposing process. In summary, Olmesartan's versatile impact on inflammation-related pathways positions it as a promising candidate for repurposing across various diseases. Ongoing clinical trials and the drug's favorable attributes enhance its appeal for further exploration and potential application in diverse medical contexts.

ABBREVIATIONS

OLM	Olmesartan medoxomil
ARB	Angiotensin II receptor blocker
ICAM-1	Intercellular adhesion molecule 1
TGF-β	Transforming growth factor β
IL-1β	Interleukin-1β
MPO	Myeloperoxidase
LDH	Lactate dehydrogenase
NF-Kb	Nuclear factor kappa B
Bcl-2B	cell lymphoma-2
MAPK	Mitogen-activated protein kinase
ERK	Extracellular signal-regulated kinase
PI3K/Akt	Phosphoinositide 3-kinase/ protein kinase B
SGLT-2	Sodium glucose transport protein 2
GLP-1	Glucagon-like peptide
ROS	Reactive oxygen species
HMGB1	High mobility group box 1
ACEI	Angiotensin converting enzyme inhibitors

Introduction

Olmesartan medoxomil (OLM) is an esterified prodrug of olmesartan. It is a drug that belongs angiotensin II receptor blockers or ARBs. It works by blocking the action of angiotensin II and is used in hypertension [1]. In the body, OLM undergoes swift conversion to its pharmacologically active metabolite, namely, Olmesartan [2]. Apart from being an ARB, it is also reported to reduce end stage renal disease in the patients of Diabetic Nephropathy [3]. Recent studies revealed that OLM possesses several pharmacological activities such as anti-cancer, anti-inflammatory, Alzheimer's' disease, and arthritis, etc., [4]. A combination of OLM with calcium-channel blockers and thiazide diuretics constitutes a deliberate and efficacious therapy. Thus, OLM can be considered an effective and safe treatment in patients with arterial hypertension and other disorders [5]. Several clinical studies showed that co-therapy of Olmesartan versus Olmesartan monotherapy effectively decreases blood pressure and reduces blood glucose levels, insulin, total cholesterol, triglyceride, and leptin [6]. OLM has been the subject of numerous trials focused on organ protection, revealing favourable outcomes in various disease markers such as microinflammation reduction, regression of plaque volume and vascular hypertrophy, and prevention of microalbuminuria [7]. It is reported that OLM treatment for eight weeks results in a higher decrease in cuff DBP (diastolic blood pressure) than subsequent treatments with losartan, valsartan, or irbesartan. It also causes a drop in cuff SBP (systolic blood pressure) which is numerically bigger than the three comparator medicines results but not statistically substantially different. Modest variations in the blood pressure-lowering effects of various ARBs may have significant long-term impacts, multiple clinical trials have shown that small changes in DBP and SBP are associated with significant reductions in the risk of serious cardiovascular events [8].

Chemistry

Olmesartan Medoxomil is a synthetic imidazole derivative with a molecular weight of 558.6 g/mol and a prodrug with an antihypertensive activity. Upon hydrolysis, olmesartan medoxomil is transformed into Olmesartan. It is stable at room temperature and in the refrigerator for ninety days. It is soluble in organic solvates but insoluble in water [9].

Pharmacokinetics of Olmesartan

OLM is well-absorbed after oral administration, with a bioavailability of approximately 26 %, taking OLM on an empty stomach is recommended to optimize its absorption. Food can reduce the bioavailability of OLM by about 40 % [10]. The pharmacokinetics are described by a two-compartment linear model that includes a first-order absorption rate and an absorption lag-time, as well as absorption rate constants (1.46h1, 0.193h1, and 0.061h1), elimination rate constants (0.189h1), and rate constants from the central to peripheral compartments (0.061h1). OLM exhibits significant protein binding (99.7 %) with a primary affinity for plasma proteins, predominantly albumin. Its extensive distribution volume suggests widespread dispersion throughout the body and ability to penetrate the blood-brain barrier is limited [11]. A bioequivalence study demonstrated that the 90 % confidence intervals for the geometric mean ratios of maximum plasma drug concentration, the area under the plasma concentration–time curve (AUC) from time 0 to the last measurable attention, and AUC from time 0 to infinity between the test and reference were all within the acceptable bioequivalence range (80 %–125 %) [12]. OLM and its metabolites are eliminated primarily in the faeces, with minimal amounts excreted in the urine. The half-life of OLM for elimination is around 12 to 14 hours. Consistent plasma levels of OLM are established within 3 to 5 days of daily administration, reaching a steady state.

Recent preclinical studies on Olmesartan

Cancer disease

In both *in vitro* and *in vivo* studies, OLM has demonstrated its ability to impede the growth of different cancer cell types, such as breast, lung, prostate, and colon cancer cells. This inhibitory effect is supposed to be connected to the suppression of the renin-angiotensin system (RAS), which plays a crucial role in developing tumours and forming new blood vessels [13]. It reduces cell proliferation by inhibiting the growth of cancer cells. Combined with Bay11–7082, it exhibits a synergistic effect, effectively blocking RAS and NF-Kb (nuclear factor kappa B) pathways. This combined action leads to significant cytotoxic activity against cancer cells, providing a vital anti-cancer effect [14]. Additionally, it has been shown to induce apoptosis in cancer cells, possibly through activating caspase enzymes and regulating Bcl-2 (B-cell lymphoma-2) family proteins. Moreover, the co-administration of Olmesartan and L-carnitine results in decreased levels of ICAM-1(intercellular adhesion molecule 1), TGF-β (transforming growth factor β), IL-1β (interleukin-1β), MPO (myeloperoxidase), lactate dehydrogenase (LDH), and oxidative stress in rats with doxorubicin-induced cardiotoxicity [15]. Furthermore, its antioxidant and anti-inflammatory activity was also confirmed in the cyclophosphamide-induced haemorrhagic cystitis model. It upregulates the Nrf2/HO-1 pathway and enhances antioxidant activities. Moreover, it hinders ROS-triggered NF-kB activation, resulting in diminished quantities of inflammatory cytokines such as TNF-α (tumor necrosis factor-α), IL-6, NF-kB, iNOS (inducible nitric oxide synthase), and COX-2 (cyclooxygenase-2) [16]. Therefore, these preclinical findings suggest that OLM may have anti-proliferative and anti-angiogenic properties. However, the evidence is not robust enough to establish OLM as a standard cancer treatment.

Inflammation disease

OLM exhibits various mechanisms to suppress inflammation and oxidative stress. It restrains the NF-κB pathway from becoming activated and lessens the expression of TNF receptor-associated factor 6 (TRAF-6) [17]. Furthermore, Olmesartan mediates the Nrf2/HO-1 signaling pathway and promotes p38-MAPK translocation, improving inflammation control and lowering oxidative stress [18]. In patients undergoing cardiopulmonary bypass, Olmesartan treatment significantly decreases IL-6 levels, highlighting its anti-inflammatory efficacy [19]. Moreover, OLM shows potential in reducing ischemia-reperfusion injury by depleting inflammatory mediators such as TNF-α, MMP-9 (matrix metallopeptidase-9), IL-6, as well as

apoptotic markers like BCL-2 and BAX [20]. In treating inflammatory bowel disease, Olmesartan downregulates gene expression, inhibits phosphorylation, and restricts nuclear translocation of p65 subunits. However, it also acts as an Nrf2 (nuclear factor erythroid 2- related factor 2) activator by upregulating Nrf-2 and HO-1 gene expression [21]. Fernandes et al. demonstrated the protective effect of Olmesartan in an intestinal mucositis model in rats, showing significant decreases in tissue levels of IL-1β and TNF-α. Furthermore, with methotrexate, OLM enhances the upregulation of SOCS-1 (suppressor of cytokine signaling-1), a protein that hinders excessive activation of the JAK-STAT signaling pathway by binding to and restraining activated JAKs. OLM also inhibits COX-2, MMP-2, MMP-9, and RANKL/RANK (receptor of nuclear factor kappa β) production, which lessens the inflammatory response [22].

Diabetic Nephropathy

Diabetic Nephropathy (DN) is the primary cause of end-stage renal disease (ESRD) [23]. It is mainly defined by the presence of proteinuria, macroalbuminuria, overt nephropathy, and clinical nephropathy [24]. The pathophysiology of DN is caused by a variety of processes, including oxidative stress and the de novo production of diacylglycerol through Protein Kinase C (PKC) activation [25]. OLM is reported to downregulate PKC gene expression and diminish the activity of inflammatory profibrotic cytokine TGF-β1. It also significantly reduces the elevated AGE levels and inhibits SIRT-1(member of sirtuin family) autophagic signaling pathways in diabetic rats [26]. The plasma creatinine levels and urinary albumin excretion is also decreased via Olmesartan in db/db mice. Histologically, it reduces glomerular hyperplasia and injury and mitigates tubular damage [27]. A triple therapy of SGLT-2 (sodium glucose transport protein 2) inhibitors, ARBs (RAS blocker), and GLP-1(glucagon-like peptide) receptor agonist is effective for renoprotection against advanced stage rapid progression of patients with diabetic nephropathy [28]. OLM was also reported to attenuate kidney fibrosis in the murine model of Alport syndrome (a hereditary type IV collagen disease with defects in postnatal maturation of glomerular basement membrane (GBM)) via suppression of tubular expression of TGF-β [29]. Moreover, combined therapy of OLM and fosinopril is said to have protective effects against diabetic nephropathy by reducing the albumin excretion from the kidney [30]. Through modulation of SIRT1-mediated podocyte viability, Olmesartan mitigates albuminuria in diabetic nephropathy. SIRT1 plays a pivotal role in regulating critical cellular processes by deacetylating transcription factors, including those involved in NF-kB-dependent inflammatory responses and PGC-1α-mediated oxidation and mitochondrial biogenesis. Given the heightened acetylation of NF-kB (p65) and PGC-1α observed in diabetic kidneys, Olmesartan may contribute to the reduction of albuminuria in diabetic nephropathy by enhancing SIRT1-mediated control over inflammation, oxidative stress, and mitochondrial dysfunction [31]. Because it falls under the renin-angiotensin system (RAS) blockers, it is expected to confer a renal protective effect. It improves renal excretory capability, reduces urinary protein-to-creatinine ratio independent of blood glucose, and increases average renal vessel lumen diameter in STZ-induced diabetic rats [32].

Reports are indicating its ability to hinder the rise in superoxide production induced by AGEs (advanced glycation end-products) and the expression of the RAGE gene. Additionally, it reversed the decline in ACE 2 mRNA levels within mesangial cells exposed to AGEs. Moreover, it eliminates the induction of VCAM-1(vascular cell adhesion molecule-1) gene expression in mesangial cells caused by AGEs, achieved through the restoration of downregulated ACE 2 levels and subsequent elevation in Ang-(1–7) production [33].

Alzheimer's Disease

Alzheimer's disease (AD) is an irreversible and progressive neurological illness and the most frequent cause of dementia in the senior population. The development of the beta-amyloid cascade and other cytoskeleton anomalies that follow the hyperphosphorylation of tau protein linked with microtubules in neurons cause a number of harmful events [34]. OLM is noted for its safeguarding influence against beta-amyloid induced neurotoxicity. It effectively mitigates increased ROS and MDA levels induced by oligomerized β-amyloid while also suppressing the heightened expression of senescence biomarkers (p16 and p21) through SIRT1-mediated deacetylation of p53 in cultured M17 neuronal cells [35]. ARBs are also reported to effectively restore insulin-mediated PI3K/Akt (phosphoinositide 3-kinase/ protein kinase B) signaling, which is sure to be defective in AD patients [36]. Angiotensin-receptor blockers are also associated with the preservation of memory and psychomotor processing speed in patients of APOE ε4 non-carriers with Alzheimer's disease. Although ACEIs are ineffective, they do not cross the blood-brain barrier [37]. A pre-treatment with a low dose of Olmesartan is reported to prevent β-amyloid-induced vascular dysregulation and impairment of hippocampal synaptic plasticity in transgenic mice (APP23 mouse) [38]. OLM slows the development of some clinical symptoms associated with metabolic syndrome, including the buildup of oxidized and ubiquitinated proteins, astrogliosis, and the conversion of astrocytes to neurotoxic forms in the brain. Moreover, it restores claudin-5 and ZO-1, i. e., markers of the structural integrity of the blood–brain barrier and synaptic protein PSD-95 [39]. The drug significantly ameliorates blood-brain barrier (BBB) disruption and reduces hippocampal oxidative stress in 5XFAD mice with chronic kidney disease in Alzheimer's disease [40]. Numerous studies propose a strong correlation between the binding affinity of ARB's receptors and the generation of Aβ. The hierarchy of receptor binding affinity is as follows: telmisartan > olmesartan > candesartan > valsartan ≥ losartan. Junjun et al. explored the distinct impacts of ARBs on Aβ generation. They observed notable increases in the Aβ42/Aβ40 ratio with Olmesartan and telmisartan, with telmisartan exhibiting the lowest percentage among the evaluated ARBs. The modulation of Aβ generation through the AT1a-PI3K pathway was attributed to telmisartan [41].

Viral Disease

COVID-19 also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic spread around the world in 2019, is reported to be most prevalent in older age, hypertension, diabetes mellitus, and cardiovascular disease patients. In addition, it has been shown that ARBs and an ACEI upregulated ACE2 expression in animal studies [42]. ARBs also have the beneficial role in the prevention and treatment of lung injury caused by COVID-19 [43]. Moreover, angiotensin-converting enzyme (ACE)2 is the main receptor for SARS-CoV-2, according to a recent study, the risk of

COVID-19 infection may be increased by elevated angiotensin-converting enzyme 2 (ACE2) expression in organs that may be targets of SARS-2. OLM reduces urine albumin excretion in an adenine mouse model but does not affect renal or pulmonary ACE2 expression. As a result of their consistent pulmonary ACE2 expression, patients with CKD may not be at increased risk of COVID-19 infection. Hence, COVID-19 patients with CKD can safely receive therapy with RAS blockers [44]. OLM also prevent renal fibrosis associated with COVID-19 patients by regulating the release of HMGB1 (high mobility group box 1) thereby, mediating the autophagic degradation of TGF-β1, leading to fibrosis [45].

Some of the recent approaches investigated the activity of OLM through computational studies. Molecular docking studies are also conducted on OLM and other ARBs against the main protease of COVID-19. Olmesartan displayed the most favorable CC50 and IC50 values (557.6 and 1.808 μM, respectively), along with a selectivity index (> 300) against the SARS-CoV-2 protease in VERO E6 cells. Several ARBs, including Fimasartan, Candesartan, and OLM, are recommended for additional preclinical and clinical evaluation for their potential activity against COVID-19 [46]. From the above studies, it is suggested that Olmesartan may be a potential candidate for the treatment against COVID-19 associated ailments, although it requires more preclinical and clinical studies.

Cardiovascular Diseases

OLM is being examined as a first-line medication and an option for people with mild to severe essential hypertension. Several clinical trials' findings showed that OLM monotherapy had the best BP-lowering effectiveness compared to other ARBs. Most of the time, triple combination therapy is preferable to component monotherapies compared to combination therapy with either HCTZ (hydrochlorthiazide) or amlodipine. In addition to having a favourable clinical profile, OLM is also reported to be more affordable than other ARBs [47]. A recent study investigates the impact of OLM on the Apelin/APJ system, Ang II/AT1 system, and aortic intimal thickening. The angiotensin II type 1 receptor's endogenous ligand, apelin, is extensively expressed in various organs, including the blood vessels, heart, kidney, and fat. In recent years, its function in cardiovascular illnesses has become increasingly scrutinized.

Apelin generates positive muscle force to prevent cardiac hypertrophy, widen blood vessels, promote blood vessel endothelial generation, reduce smooth muscle cell proliferation, and resist atherosclerosis through binding with APJ on the heart and vasculature endothelial cells. Following balloon injury, OLM mitigated the activation of extracellular signal-regulated kinase (ERK) signaling, leading to reduced proliferation of vascular smooth muscle cells and diminished intimal thickening. Additionally, Olmesartan elevated Apelin and APJ expression while concurrently decreasing the expression of Ang II and AT1 [48].

Clinical Perspective of Olmesartan

Some recent clinical studies related to Olmesartan monotherapy and in combination are as follows.

Cardiovascular disorders

Nowadays, high blood pressure is the prevailing disorder, and adopting an early and effective control strategy for it can be seen as a promising therapeutic approach to alleviate the future burden of cardiovascular diseases associated with hypertension. Clinical data regarding the effectiveness and safety of five prominent categories of antihypertensive medications, such as ACE inhibitors, ARBs, beta-blockers, calcium antagonists, and diuretics, have emerged recently. Notably, these studies have revealed that ARBs, in particular, exhibit dose-dependent reductions in blood pressure and are well-tolerated by hypertensive children and adolescents [49]. An evaluation of the effectiveness and safety of a fixed-dose combination (FDC) therapy comprising Olmesartan medoxomil (40 mg) and rosuvastatin (20 mg) was carried out in a clinical study involving Korean patients with mild to moderate hypertension and dyslipidemia. After eight weeks of treatment, the LDL cholesterol levels in the FDC group were considerably lower than those in the OLM group in terms of percentage change from baseline (− 52.3 % [2.8 %] vs − 0.6 % [3.5 %], P0.0001), with a difference of − 51.7 % (4.1 %). The findings of this study establish that combining OLM and rosuvastatin in FDC therapy presents a secure and efficacious treatment choice for individuals dealing with hypertension and dyslipidemia [50]. In a real-world clinical setting, Park and colleagues evaluated the effectiveness and safety of a single pill combination (SPC) containing OLM/AML/HCTZ involving 9,749 Korean patients diagnosed with essential hypertension. The results demonstrated that over 74 % of the patients achieved significant reductions in both systolic and diastolic blood pressure, irrespective of risk factors such as diabetes, cardiovascular diseases, or chronic kidney disease (CKD). Notably, patients with cardiovascular diseases and those aged > 65 years exhibited a significantly higher rate of treatment success (p ≤ 0.05) [51]. In a phase III study characterized by randomization, double-blinding, and up-titration, the combination of Olmesartan medoxomil 40 mg and HCTZ 12.5 mg demonstrated a significant decrease in mean seated diastolic blood pressure (SeDBP) by 18.9 mmHg and mean seated systolic blood pressure (SeSBP) by 5.4 mmHg (p < 0.0001). This effect was significantly greater than that of Olmesartan medoxomil 40 mg alone, which resulted in a reduction of SeDBP by 15.8 mmHg (difference: − 3.1 mmHg, p < 0.0001) after 8 weeks of treatment [52]. In everyday clinical practice, OLM is frequently recommended as a standalone treatment or adjunct therapy, effectively lowering blood pressure in Indian patients with essential hypertension, including those with concurrent diabetes [53].

A satisfactory therapeutic outcome was observed in ninety patients with a history of hypertension and ischemic stroke who were treated with a combination of clopidogrel bisulfate tablets and OLM. The combination decreased the long-term stroke recurrence rate in the 12-month study, and the AT1R level may significantly impact patients' prognoses [54]. Based on the above studies it is evident that OLM may be repurposed in many cardiovascular diseases other than hypertension such as Ischemic stroke, cardiomyopathy etc.,

Diabetes

In clinical practice, ARBs have been advised to mitigate microalbuminuria in individuals with diabetes mellitus. Moreover, they have effectively diminished cardiovascular incidents and mortality rates among those with ischemic heart disease. OLM, along with other ARBs, can be an option for hypertension and other diseases such

as chronic kidney disease, cerebrovascular events, heart failure, diabetes, or ischemic heart disease [55]. When considering diabetic nephropathy, microalbuminuria serves as an early biomarker, and OLM has demonstrated the capability to postpone or avert its onset in individuals with type 2 diabetes and normoalbuminuria. In a clinical study encompassing 4447 participants, the incidence of microalbuminuria emergence was found to be 8.2 % in the OLM group (178 out of 2160 evaluable patients), in contrast to 9.8 % in the placebo group (210 out of 2139 patients). Moreover, the utilization of OLM extended the time to microalbuminuria onset by 23 % [56]. Supporting these findings, a recent trial involving 80 patients demonstrated that a combination treatment of OLM and amlodipine for 24 weeks resulted in a significant decrease in systolic and diastolic blood pressures by more than 18 mmHg and 8 mmHg, respectively. Furthermore, OLM treatment led to an increase in serum Ang-(1–7) levels (25.8 ± 34.5 pg/mL to 46.2 ± 59.4 pg/mL), surpassing the effect of amlodipine treatment (29.2 ± 38.9 pg/mL to 31.7 ± 26.0 pg/mL). Notably, the reduction in albuminuria was significantly associated with the elevated levels of ACE2 and Ang-(1–7). The improvement in microvascular function was mainly linked to the changes in Ang-(1–7) levels ($r = 0.241$, $P < 0.05$) [57]. An open-label Phase II study was conducted to investigate the effects of Olmesartan Medoxomil in normotensive patients with Diabetic Nephropathy. The study spanned 16 weeks, with an initial dose of 5 mg that was gradually adjusted to 10 mg, 20 mg, and 40 mg after confirming tolerance at weeks 4, 8, and 12. The primary efficacy endpoint was the alteration in urinary protein/creatinine ratio from baseline to the treatment's conclusion. The patient's creatinine clearance was also assessed as a secondary endpoint [58]. Later, OLM potency, efficacy, and safety compared to a placebo on the development of diabetic renal disease were assessed in a Phase III trial called ORIENT [59]. A clinical study named randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) supported that OLM versus placebo delayed microalbuminuria onset in patients with type 2 diabetes and normoalbuminuria [60]. Thus, it is clear from the research above that OLM may be repurposed to treat diabetes-related problems, particularly diabetic nephropathy, but further clinical research is needed.

Dilated Cardiomyopathy (OVOID trial)

A randomized clinical trial with a parallel-group design was conducted to investigate the effects of Olmesartan and Valsartan on myocardial metabolism in patients diagnosed with Dilated Cardiomyopathy (DCMP). The problem was open-label and non-blinded. A total of 40 patients, aged 20–85 years, were randomly allocated into the OLM or the valsartan group. This was the first study to examine the advantages of a 6-month OLM medication on individuals with DCMP's myocardial metabolism. Furthermore, OLM has vasodilatory and organ-protective actions, including the suppression of vascular remodeling and cardiac hyperplasia. If the prospective effects of OLM on cardiac metabolism are demonstrated, the findings of this investigation may point to the unique impact of ARBs as a metabolic treatment [61].

Bioequivalence Study

A randomized Phase 1 bioequivalence study was carried out using two distinct formulations of OLM in healthy participants following a single oral dose administration under fasting conditions. The study's main outcomes focused on the pharmacokinetic parameters, specifically C_{max} and AUC_{0-t} of Olmesartan [62]. Further, single dose, Phase I study was initiated to determine the bioavailability of Olmesartan Medoxomil/Hydrochlorothiazide 40 mg/25 mg film-coated tablets in healthy adults with the pharmacokinetic parameters, i. e., C_{max} and AUC_{0-t} of olmesartan and hydrochlorothiazide [63].

The details of the ongoing clinical trial of Olmesartan on different diseases are given in ▶ Table 1.

Interplay between RAS, ROS, NRF2, COX, and NfkB

Previous research has revealed numerous mechanisms, including the interaction of hyperglycemia, NRF2 induction, cellular oxidative stress, renin-angiotensin system (RAS) activation, NF-kB and MAPK pathways. There is an indication that NRF2 localization towards the nucleus is hindered in the setting of increased oxidative stress. This defect obstructs NRF2 from properly promoting antioxidant gene expression, limiting cellular antioxidant defense systems. Consequently, there is a disparity between the production of oxidants and the body's capacity to neutralize them. Increased oxidative stress can be caused by reduced NRF2 activation and consequent declines in antioxidant gene expression.

The RAS pathway has been demonstrated to be activated by oxidative stress, largely through ROS. Elevated oxidative stress can cause renin release, which starts the RAS cascade. Angiotensin-II is produced by RAS activation and interacts with the AT1 receptor, activating NADPH oxidase. NADPH oxidase is a crucial producer of reactive oxygen species (ROS) in several different cell types, including immunological cells, endothelial cells, and vascular smooth muscle cells. The AT1 receptor increases NADPH oxidase, increasing the generation of ROS, notably superoxide anions (O2). ROS, such as superoxide anions and hydrogen peroxide, can activate upstream signaling pathways implicated in NF-B activation, either directly or indirectly. Oxidative stress plays a significant role in inflammation and cell damage through different mechanisms like activation of NF-κB, MAPK (mitogen-activated protein kinase) pathways, and lipid peroxidation.

ROS, in particular, can activate IB kinase (IKK), causing inhibitory IB proteins to degrade and releasing NF-B dimers (p50 and p65) into the inhibitory complex. The produced NF-B dimers subsequently translocate into the nucleus, where they control the transcription of target genes that regulate inflammation, immunological reactions, and cell survival.

NF-B can directly attach to the COX-2 promoter region, triggering transcription. COX-2 is an enzyme that produces prostaglandins, notably prostaglandin E2 (PGE2). When COX-2 is activated, it makes more prostaglandins, which may lead to pain, inflammation, and other cellular reactions.

NF-κB activation can also regulate the expression of MAPK pathway components, such as MAP3Ks and MAP2Ks. This regulation can activate specific MAPK cascades, including extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), and p38 MAPK. The interplay between NF-κB and MAPK pathways modulates cellular responses, including immune and inflammatory processes.

▶ **Table 1** List of Ongoing and completed Clinical trials of Olmesartan.

S. No	Tittle	Status	Condition	Dosage regimen	Refer-ence
1.	Efficacy and Safety Study of the Fixed-dose Combination of Olmesartan + Indapamide When Compared to the Isolated Drugs in the Treatment of Hypertension. (OLINDA)	Not yet recruiting (Phase 3)	Essential Hypertension	Drug: fixed dose of olmesartan 20 mg/40 mg + indapamide 1,5 mg Drug: Isolated drugs Olmesartan (20 mg or 40 mg) and Indapamide (1,5 mg)	[64]
2.	Effect of Olmesartan on Angiotensin (1–7) Levels and Vascular Functions in Diabetes and Hypertension (Ang(1–7))	Recruiting (Phase 4)	Angiotensin/ Aldosterone Hypertension Type 2 Diabetes Mellitus	Drug: Olmesartan	[65]
3.	The Bioequivalence Study of Two Different Formulations of OlmesartanMedoxomil/ Hydrochlorothiazide after a Single Oral Dose Administration Under Fasting Conditions.	Unknown (Phase 1)	Bioequivalence	Drug: Olmesartan Medoxomil/ Hydrochlorothiazide 40 Mg/25 Mg film-coated tablets for oral use Drug: Olmetec® Plus 40 Mg/25 Mg film-coated tablets for oral use	[63]
4.	Combination of Olmesartan Effect on Myocardial Viability of Patients With Dilated Cardiomyopathy	Unknown (N/A)	Dilated Cardiomyopathy	Diagnostic Test: FDG PET	[61]
5.	Effect of Olmesartan and Nebivolol on Ambulatory Blood Pressure and Arterial Stiffness in Acute Stage of Ischemic Stroke	Completed (Phase 2)	Stroke, Ischemic	Drug: Olmesartan Drug: Nebivolol Other: No antihypertensive treatment	[66]
6.	The Effect of Rosuvastatin and Olmesartan on the Progression of Coronary Atherosclerotic Disease	Unknown (Phase 2)	Coronary Syndrome	Drug: Rosuvastatin Drug: Olmesartan Drug: Combination (and 3 more...)	[67]
7.	Efficacy and Safety of Olmesartan Associated With Chlorthalidone in Essential Arterial Hypertension Control	Not yet recruiting (Phase 3)	Essential Arterial Hypertension	Drug: Olmesartan Medoxomil 20 mg + Chlorthalidone 12,5 mg Drug: Olmesartan medoxomil 20 mg + Chlortalidone 25 mg Drug: Olmesartan 20 mg + hydro-chlorothiazide 12,5 mg	[68]
8.	A Clinical Trial to Evaluate the Efficacy and Safety of Olmesartan/Amlodipine/Rosuvastatin Combination Treatment in Patients With Concomitant Hypertension and Hyperlipidemia	Completed (Phase 3)	Hypertension Hyperlipidemia	Drug: Amlodipine/Olmesartan 10/40 mg (Combination drug), Rosuvastatin 20 mg Drug: Olmesartan 40 mg, Rosuvastatin 20 mg Drug: Amlodipine/Olmesartan 10/40 mg (Combination drug)	[69]
9.	Observational Study to Evaluate the Effect of Improving Systolic BP and LDL-C Compared to Conventional Treatments and the Convenience of Taking Medication of Olostar Tab	Not yet Recruiting	Hyperlipidemias Hypertension	Drug: Rosuvastatin, OlmesartanMe-doxomil	[70]
10.	Clinical Trial to Evaluate the Efficacy and Safety of OLOMAX Tab in Hypertension Patients With Low-Intermediate Risk for Cardiovascular Disease	Completed (Phase 4)	Hypertension Dyslipidemia	Drug: OLOMAX 20/5/5 mg Drug: OLOMAX 20/5/10 mg Drug: Olmesartan 20 mg/ Amlodipine 5 mg	[71]

According to oxidative stress, reactive oxygen species can peroxidize cellular lipids, producing malondialdehyde (MDA). Increased MDA production can compromise cellular integrity and lead to oxidative stress-related cellular damage.
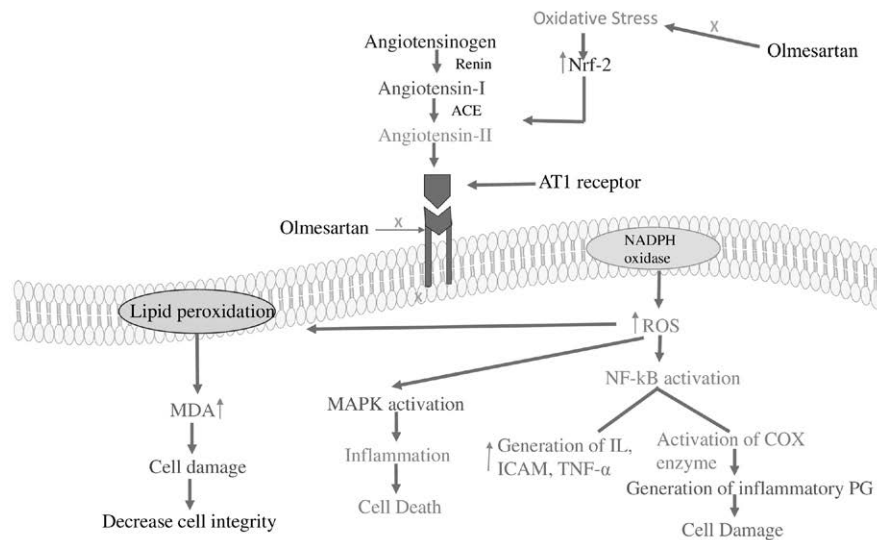
Hypothesis

Olmesartan, an Angiotensin receptor-1 (AT-1) blocker, possesses multifaceted effects on oxidative stress, inflammatory pathways, and cellular membrane integrity. By antagonizing the AT-1 recep-tor, Olmesartan can suppress NADPH oxidase activation, leading to a reduction in ROS production and mitigating oxidative stress in cells and tissues. This action is crucial in preventing lipid peroxidation, which generates MDA and jeopardizes cellular membrane integrity. The inhibition of oxidative stress and lipid peroxidation by Olmesartan contributes to the protection of cellular membranes, thereby preserving structural integrity.

Additionally, Olmesartan exhibits anti-inflammatory effects through modulation of COX, NFκB, and MAPK pathways. NFκB, a

► Fig. 1 Proposed hypothesis of Olmesartan combating Inflammation and oxidative Stress. Olmesartan being an Angiotensin receptor-1 (AT-1) blocker can inhibit the increased oxidative stress by suppressing NADPH oxidase enzyme. Furthermore, it can modulate the inflammatory mediators like nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB), Mitogen-activated protein kinases (MAPK), and Cyclooxygenase (COX). Olmesartan also protects cellular membrane integrity by inhibiting lipid peroxidation and the formation of Malondialdehyde (MDA).

pivotal transcription factor in inflammatory gene expression, is regulated by Olmesartan, leading to the downregulation of pro-inflammatory genes and a suppression of the inflammatory response. Notably, Olmesartan interferes with the direct binding of NF-κB to the COX-2 promoter, inhibiting the transcription process. COX-2, responsible for synthesizing prostaglandins like prostaglandin E2 (PGE2), undergoes reduced activation by Olmesartan, curbing the production of prostaglandins associated with pain, inflammation, and cellular reactions.

Moreover, Olmesartan influences specific MAPK cascades, including ERK, JNK, and p38 MAPK, affecting cellular responses in immune and inflammatory processes. The interaction between NF-κB and MAPK pathways under the influence of Olmesartan further regulates immune and inflammatory responses.

By inhibiting NFKB and COX-mediated activation of proinflammatory cytokines, Olmesartan orchestrates a comprehensive anti-inflammatory and antioxidant effect. However, unraveling the precise molecular mechanisms and clinical implications necessitates further exploration through rigorous experimental studies and clinical trials (► **Fig. 1**).

This shows that Olmesartan might be an effective treatment option for inflammatory disorders, cancer, diabetic nephropathy, and neuropathy. However, more study is needed to test these hypotheses and investigate Olmesartan's specific processes and therapeutic consequences in these circumstances.

Conclusion

In this comprehensive review, we delve into recent preclinical and clinical trials on Olmesartan, revealing its significant efficacy across a spectrum of diseases. Preclinical studies demonstrate the drug's prowess in reducing key inflammatory markers such as ICAM-1, TGF-β, IL-1β, and COX, showcasing its potential therapeutic impact. Notably, Olmesartan emerges as a prospective treatment option for diverse conditions, including ulcerative colitis, Alzheimer's disease, and cancer.

Beyond its anti-inflammatory effects, Olmesartan exhibits versatility by downregulating PKC gene expression and curbing the activity of the pro-fibrotic cytokine TGF-β1. This multifaceted profile positions Olmesartan as a promising medication with broad applications, particularly in the realms of hypertension and inflammation. The promising outcomes from these trials suggest that Olmesartan could play a pivotal role in addressing various diseases, necessitating forward-thinking approaches for its integration into therapeutic strategies.

As we look ahead, the futuristic potential of Olmesartan calls for continued exploration and innovative approaches in drug development. The versatility demonstrated by Olmesartan opens avenues for its implementation in treating diverse conditions, paving the way for a more nuanced and effective approach to managing complex diseases.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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