CDDO and Its Role in Chronic Diseases

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Abstract There has been a continued interest in translational research focused on both natural products and manipulation of functional groups on these compounds to create novel derivatives with higher desired activities. Oleanolic acid, a component of traditional Chinese medicine used in hepatitis therapy, was modified by chemical processes to form 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO). This modification increased anti-inflammatory activity significantly and additional functional groups on the CDDO backbone have shown promise in treating conditions ranging from kidney disease to obesity to diabetes. CDDO's therapeutic effect is due to its upregulation of the master antioxidant transcription factor Nuclear factor erythroid 2-related factor 2 (Nrf2) through conformational change of Nrf2-repressing, Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1 (Keap1) and multiple animal and human studies have verified subsequent activation of Nrf2-controlled antioxidant genes via upstream Antioxidant Response Element (ARE) regions. At the present time, positive results have been obtained in the laboratory and clinical trials with CDDO derivatives treating conditions such as lung injury, inflammation and chronic kidney disease. However, clinical trials for cancer and cardiovascular disease have not shown equally positive results and further exploration of CDDO and its derivatives is needed to put these shortcomings into context for the purpose of future therapeutic modalities.

Keywords CDDO · dh404 · TFEA · Nrf2 · Bardoxolone · CDDO-Me · CDDO-Im · Vascular · Hepatotoxic · Cardiorenal · Apoptosis · Keap1

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Definitions

CDDO	2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid
CDDO-Im	CDDO imidazolide
CDDO-Me	CDDO-methyl ester
CDDO-dhTFEA	CDDO-dihydrotrifluoroamide

1 Introduction

Triterpenoids are natural saponin compounds (such as cholesterol and phytosterols) with a multi-carbon skeleton that can be manipulated synthetically, adding various chemical groups for functionality. CDDO, or 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, is a synthetic triterpenoid derived from oleanolic acid that was purposely constructed for anti-inflammatory purposes in macrophages and has, over time, been modified with methyl, amine, and imidazolide groups to further affect various signaling pathways such as FLIP/TRAIL, caspase, SMAD, and mTOR. However, the primary target of CDDO and its related compounds is the Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1 (Keap1) that regulates nuclear factor erythroid 2-related factor 2 (Nrf2) that, in turn, acts as a master transcription factor for upregulation of antioxidant response genes such as heme oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase (NQO1). Modulation of Nrf2 by CDDO and related compounds has been repeatedly shown in the literature to positively affect a multitude of disease states in animal models, including amyotrophic lateral sclerosis (ALS), various cancers (breast, prostate, etc.), inflammatory shock, and cardiovascular damage. Phases I and II trials with CDDO in chronic kidney disease have shown much promise. However, well-controlled Phase I cancer trials in humans have not shown dramatic improvements in the disease outcomes. The reasons for these variable results are not well understood, and much work remains to be done in determining the minute details of CDDO-affected signaling pathways in humans. This review will explore a wide range of the literature to provide a framework of understanding about CDDO's chemical properties, its signaling targets, and therapeutic efficacy in animal models. Although CDDO compounds may not yet be the "silver bullet" for some diseases, the clear effect of CDDO treatment on crucial cellular pathways in multiple disease models makes it useful in the laboratory and more work may yet find a derivative compound that proves efficacious in treating human disease.

2 Chemical Properties and Pharmacokinetics

2.1 Chemical Synthesis and Characteristics

Oleanolic acid has been used in China as a therapy for hepatitis and serves as the backbone of CDDO [1]. CDDO was first reported in a series of papers by Honda et al. that stepwise-converted oleanolic and ursolic acids into a compound capable of both inhibiting inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) production in mouse macrophages and growth in an NRP.152 prostate cell line [2–4]. CDDO was originally synthesized from modification of the A and C rings of the saponin compounds with 1-en-3-one functionality, but the C-2 position was found to be critical for activity of the compound [3]. Further studies revealed that α,β-unsaturated carbonyl moieties boost the effect of the compound by several fold [5]. Briefly, oleanolic acid was formylated in the presence of sodium methoxide, with tetrahydrofuran (THF) added. After an isoxazole intermediate was formed via methoxide cleavage and alkali hydrolysis, the nitrile intermediate. A nitrile intermediate was reacted in dimethylfuran (DMF) with lithium iodide in a halogenolysis reaction to form CDDO [3]. A later report from Fu and Gribble [6] introduced a scalable and much more efficient synthesis protocol for CDDO-Me that could prove useful in clinical studies. The polar structure of CDDO lends well to solubility in DMSO for the laboratory while human trials used microcrystalline preparations in gelatin capsules [7]. Functional groups can be added to CDDO, such as a C28 methyl ester, imidazolide, and various amides (ethyl, diethyl, and trifluoroethyl amides) [8, 9]. Each of these compounds has specific kinetics and, taken as a whole group, offer an arsenal of compounds to test in the laboratory.

2.2 Pharmacokinetics of CDDO

CDDO, as synthesized by Honda and Suh [3], has an IC50 of just 0.0004 μM in mouse macrophages, over a thousand times stronger than its parent compound oleanolic acid. Derivatives such as CDDO-Me and CDDO-Im have induced strong NQO1 activity at single doses of as little as 10 μmol/kg in mice while other reports have seen 5–130 nM inhibitory effects in tumor cell lines with CDDO amides [8, 9].

A study undertaken by Noker et al. [10] in rats and dogs found that CDDO is eliminated from plasma in 2 stages, with a mean half-life of 0.06 h for α-phase and 1.95 h for β-phase in rats with total clearance being roughly 9 L/m^2/h. Dogs showed a much faster clearance with an α-phase of 0.02 h and a β-phase of 0.65 h with a total clearance of 44.6 L/m^2/h [10] Total results indicated linear pharmacokinetics with side effects (diarrhea, piloerection) but no toxicity even at doses of 50 mg/m^2/h with total maximum tolerated dosages of 2160 mg/m^2 in rats and 6000 mg/m^2 in dogs [10]. This low toxicity with lack of catastrophic side effects makes CDDO an ideal compound for in vivo animal studies. Further studies on

Table 1 Animal studies involving CDDO

Drug	Animal model	Studies and references
CDDO-Me	Murine	Lung injury [125], tumor vaccination [106], colon cancer [93, 126], breast cancer [101, 102], lung cancer [99, 127, 128], pancreatic cancer [129], prostate cancer [35, 94, 103], Leukemia [87], immunosuppression [130], kidneys [41, 80], nephritis [77], gene profiling [8, 26, 78, 109, 131]
CDDO-Im	Murine	Obesity [65], gene profiling [52], chondrogenesis [62], kidneys [76], lung cancer [99, 127], colitis [132], liver damage/hepatotoxicity [98, 133–135], immune neoplasms [46], retinal death [89, 91], neural ischemia [136], diabetes [137]
CDDO-TFEA/CDDO-EA	Murine	Retinal injury [59], ALS [138], lung cancer [99], Liver injury [133, 139]

methodology for bioanalytical methods for in vivo studies with CDDO found that its electrophilic nature caused it to react with glutathione (GSH) and nucleophilic groups in proteins as well as *N*-acetylcysteine, forming covalently adducted metabolites that can be measured with protein precipitation, Edman degradation, and ammonium hydroxide [11]. Clearly, CDDO's main mode of chemical action is for the functional electrophilic groups to attack sulfhydryl and cysteine moieties on target proteins. A clinical trial in humans by Hong et al. [7] explored the more complex pharmacokinetics in chronic kidney disease patients treated with CDDO-Me, finding a maximum tolerated dosage to be 900 mg/day and a maximum peak plasma time of 4 h with a mean half-life of about 39 ± 20 h. Hong et al. concluded that 900 mg/day was the appropriate dosage for any further Phase II trials. Clinical testing has been done in human volunteers with an amorphous spray-dried dispersion (SDD) microcrystalline version of CDDO-Me to increase bioavailability and this was found to be superior in bioavailability to the microcrystalline version used in the Hong trial [12] (Table 1).

3 Signaling Pathways Affected by CDDO

3.1 Antioxidant Response and Nrf2 Regulation

Although CDDO compounds may directly interact with proteins in multiple signaling pathways, the primary mode of CDDO action is the upregulation of Nrf2. Nrf2 is in the Cap "n" Collar (CNC) family of basic leucine zipper (bZip) transcription factors constitutively expressed in the cell and resident in the cytoplasm [13, 14]. The forked Keap1, a substrate adaptor of the E3 ubiquitin ligase Cullin3 complex, contains two large spheres (β-propeller regions) that repress Nrf2

constitutively and represents the most popular target of treatments to modulate Nrf2 activity [15–17]. Upon ubiquitination, Nrf2 is rapidly degraded by the proteasome, but CDDO (and some other small electrophilic molecules) can bind to a key cysteine residue in the Broad complex, Tramtrack, and Bric-a-Brac (BTB) domain of Keap1 to inhibit ubiquitination and proteasomal degradation of Nrf2 [15, 18–20]. Other signaling pathways of Keap1 regulation have been reported, specifically that $p21^{Cip1/WAF1}$ can compete with Nrf2 for Keap1 binding, increasing levels of free Nrf2 to localize to the nucleus and that p62 directly binds to Keap1 on three specific arginine residues to inhibit Keap-1-mediated Nrf2 ubiquitination (linking Nrf2 and autophagy) [21, 22]. Whether or not these alternate pathways may be affected by CDDO is still unclear. If Keap1 is active, the half-life of Nrf2 is very short, on the order of about 20 min [23]. Although this may make probing for nominal levels of Nrf2 difficult, the rapid turnover allows for rapid response. Once translocated to the nucleus, Nrf2 binds with the adaptor protein Maf and binds to antioxidant response elements (ARE) which attracts CREB and p300 to form a complex that can attract RNA polymerases to transcribe antioxidant genes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), gamma-glutamylcysteine synthetase (γ-GCS), HO-1, and NQO1 [13, 24–27]. The Keap1-Nrf2 axis in antioxidant response has been extensively reviewed and, as CDDO has a potent ability to effect a conformational change in Keap1 to reduces its ability to catalyze Nrf2 for K48 ubiquitination, this axis serves as the basis for CDDO's use in disease therapy models [13, 16, 24–26, 28]. Therefore, it is safe to say that any use of CDDO will involve Nrf2 as an upstream modulator of genes of interest, made possible by Nrf2's master ability to affect downstream pathways by ARE activity. Note that natural compounds such as α-lipoic acid and polyphenols like quercetin have also been extensively shown to increase Nrf2 activity by upstream pathways such as PI3 K/Akt, especially in liver and cardiovascular studies [29–33] (Fig. 1).

4 Reactive Oxygen Species and Cell Death: The Primary Target of CDDO

4.1 Apoptosis and Necrosis: CDDO Affects Cell Death via Nrf2

The two known types of cell death are apoptosis and necrosis. Cellular damage from reactive oxygen species (ROS) or nitrogen species (NOS) can affect mitochondria, membranes, and cell nuclei, triggering checkpoint genes such as p53 to induce apoptosis or system wide damage, resulting in necrosis [34]. In apoptosis, death occurs in an "implosive" style with programmed and sequential events shutting down the cell to avoid damage to surrounding cells. Necrosis, on the other hand, can be considered "explosive," where cellular debris (especially highly reactive mitochondrial cytochrome c) and cytokine release cause inflammation and

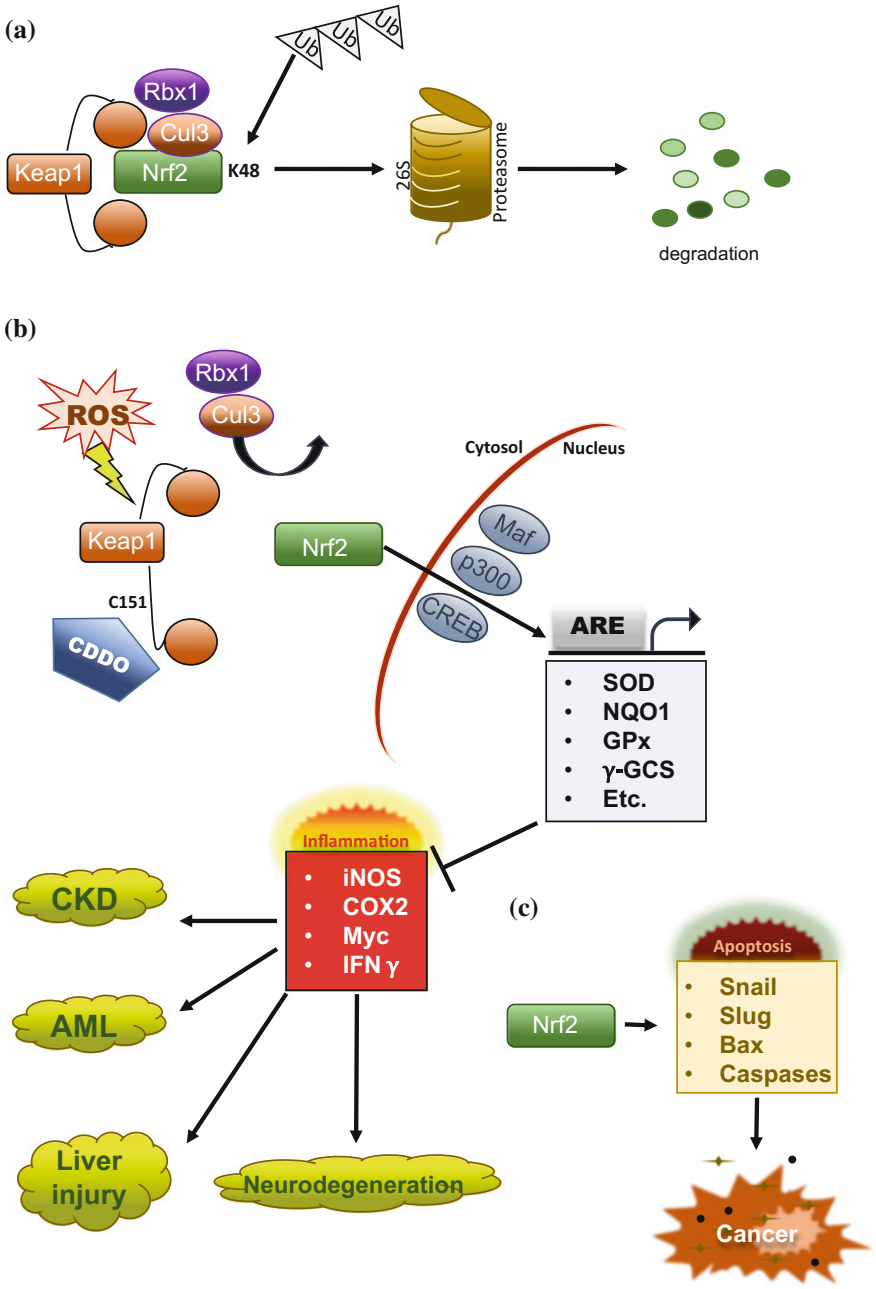

Fig. 1 **a** The Keap1-Nrf2 regulatory pathway features Cul3-mediated K48-linked polyubiquitination of Nrf2, causing subsequent degradation in the proteasome. **b** Damage by ROS or interaction with CDDO on Cysteine 151 of Keap1 releases Nrf2 to the nucleus, where it upregulates antioxidant protective factors that can counter inflammation and related disease states. **c** Nrf2 regulates many apoptotic factors in cancer cells that it does not in healthy cells. This may be due to defects in cellular metabolism that render cancer cells uniquely vulnerable to Nrf2-mediated apoptosis

damage to cascade into surrounding tissue [35]. Nrf2 is directly involved in reducing necrotic cell death by upregulation of antioxidant factors such as HO-1, super oxide dismutase (SOD), and NQO1, but can actually cause apoptosis in cancer cells by affecting the upregulation of apoptotic factors such as Snail, slug, TCF-/ZEB1, and Bax [27, 36]. If Nrf2 can control so many factors critical in apoptosis and necrosis, it stands to reason that upregulation of Nrf2 by CDDO compounds may provide protection and/or ablation of cytotoxic ROS-induced death in normal cells while causing cancerous or abnormal cells to die.

In prostate cancer cells, CDDO-Me was reported to activate caspases 3, 8, and 9 while disrupting NF-κB signaling through direct inhibition of iκB kinase, killing the cancer cells [37, 38]. It was also documented that CDDO-Me induced prostate cancer cell death via suppression of Akt [39]. Similar results were found in ovarian cancer cells and rat kidney reperfusion injury [40–42]. In acute myeloid leukemia (AML) cells, CDDO-Me has been reported to suppress phosphorylation of ERK1/2 through the activation of p38/MAPK (43). Intriguingly, another report showed that, in AML, CDDO-Me could sensitize cells to pro-apoptotic TRAIL while downregulating anti-apoptotic FLIP levels and that CDDO strongly upregulates caspase 8 [44, 45]. In iMycEμ mice that are prone to B and plasma cell neoplasms (viz. lymphoma), CDDO-Im treatment caused upregulation of Fmo4 and P450 oxygenases with down-regulation of c-Myc and apoptosis [46]. Yates et al. demonstrated that CDDO-Im mitigates the aflatoxin-induced oxidative stress in the liver with an increase in GSTA2, GSTA5, AFAR, and EPHX1 antioxidant genes [47, 48]. Bey et al. [49] reported that NQO1, which is a primary transcriptional target of Nrf2 and is upregulated upon CDDO treatment, is required for PARP1-programmed necrosis in breast cancers, which can be apoptosis resistant. On the flip side of ROS-induced injury and cellular protection, Li et al. [50] have reported that doxorubicin-induced cardiac necrosis can be ameliorated by Nrf2 increases. Treatment with CDDO could provide the increased Nrf2 necessary to ablate doxorubicin-induced cardiac injury. In the normal liver, caspases intimately associated with apoptosis and necrosis have been shown to be downregulated by lipoic acid which activates Nrf2, especially caspase-3 [31]. In normal hearts and in early-stage heart disease, Nrf2 is also very protective [16, 27, 51]. It is therefore important to note that CDDO compounds in published studies show protective effects to normal or injured cells but kill cancerous cells. Interestingly, a report that compared Keap1 knockout mice to CDDO-Im-treated mice show that both genetic and pharmacological activation of Nrf2 regulates many metabolism genes, including lipid and carbohydrate metabolism (particularly the pentose phosphate pathway to sustain Nrf2 activity) [52, 53]. This indicates that cancerous cells, which often show defects in metabolic pathways, may be adversely affected by Nrf2 upregulation forcing upregulation of apoptotic factors in these and not normal cells or cells with minor injury. In fact, a recent report by Qin et al. [54] has found a solid link between the action of Nrf2 and the functional status of autophagy: Nrf2 activation is cardioprotective when myocardial autophagy is intact whereas Nrf2 acts as a mediator of cardiac maladaptive remodeling and dysfunction when myocardial autophagy is impaired. Bernstein et al. showed a similar effect in B-cell lymphoma cells via CDDO treatment/Nrf2 activation and inhibition of the Lon protease system, which clears mitochondrial proteins [55–57].

This proves that a critical link exists between metabolism (specifically autophagy) and the effect of Nrf2 on a cell. Upon Nrf2 activation, normal cells (and even the retina) with normal autophagic function receive protection in the form of upregulated antioxidant defense while abnormal cells with autophagy impairment may see deleterious effects [58, 59]. Other oleanolic acid derivatives have also been shown to cause this induction of autophagy in normal cells that, in cells with dysfunctional autophagic machinery, can cause early death [60, 61].

5 Other Targets of CDDO: Heat Shock Protein, Telomerase, and MTOR

Although the strongest transcriptional effects from CDDO treatment come from Nrf2 activation, there have been several other direct targets reported in the literature. Suh et al. [62] reported that CDDO-Im and CDDO-ethyl amide were able to induce chondrogenesis in newborn mice by upregulating SOX9 and collagen. However, as there was no in-depth exploration as to the effect of Nrf2 on these genes, it is yet unclear as to whether or not CDDO had direct effects on upstream elements in the chondrogenic pathway. Telomerase (hTERT) activity is a critical part of cancer cell proliferation and there is a report that CDDO-Me targets hTERT in prostate cancer cells, with knockdown of hTERT increasing apoptosis upon CDDO treatment [63]. Heat shock protein 90 (hsp90) was found by Qin et al. [64] to directly target hsp90 in an ovarian cancer cell model, inhibiting it and reducing cell proliferation. This was shown by thermal shift assay and can be blocked by dithiothreitol [64]. Although several putative targets have been reported, only the hsp90 interaction has been shown to be a direct effect of CDDO and not as a Nrf2-mediated effect. Although these several reports have shown some potential of CDDO to target alternate pathways directly, the majority of evidence points to a primarily Nrf2-mediated mechanism of action. However, the specificity of CDDO for Nrf2 makes it useful in isolating Nrf2-related pathways and mechanisms with little interference from other upstream regulators.

6 Diseases

The goal of CDDO as a therapy is to exploit its ability to upregulate Nrf2 and Nrf2's ability to protect healthy cells from necrosis while destroying abnormal ones by apoptosis. Because CDDO and its derivatives are fairly nontoxic, they lend themselves well to testing as therapies for various diseases.

6.1 Cardiac Disease/Vascular Dysfunction

Much work has been done in animal models with CDDO in the prevention of cardiopulmonary disease and injury. Sussan et al. [16] reported that, in mice, cigarette smoke-induced cardiac dysfunction and emphysema modeling chronic obstructive pulmonary disease (COPD) could be reduced by CDDO-Im treatment. CDDO-Im has also been shown to ameliorate obesity in mice fed a high-fat diet, showing potential for reducing a major cause of cardiovascular disease [65]. CDDO could also play a key role in attenuating lesion formation and loss of tone in vascular disease, especially as FLIP/TRAIL and Myc, lesion forming factors regulated by Nrf2, play a role in VSMC-mediated neointimal formation [46, 66–68]. Wang reviews several preclinical trials that indicate that CDDO-Me can reduce blood vessel inflammatory responses by regulating the endothelin pathway and that this may be due to involvement of NF-κB in the endothelin pathway which Nrf2 can counter [69]. It is well established in the literature that iNOS and cytokines like IFNγ produced by macrophages activated by periodontal diseases or LPS can cause inflammatory damage in blood vessels, recruiting more macrophages in an M1 response and amplifying vascular damage [3, 70, 71]. CDDO-dhTFEA (dh404) and CDDO-Me have been shown to suppress the inflammatory responses in macrophages, thereby providing protection to the vascular system [71, 72]. Regarding future cardiac studies, vital cardiac adaptation has been shown to rely on a Nrf2/autophagy axis, while clearance of toxic proteins relies on Nrf2, making CDDO treatment a distinct possibility to upregulate those protective features [51, 73].

Studies in humans with CDDO compounds have been completed up to Phase II. A review by Wang lists several Phase I studies that evaluated several pharmacokinetic parameters of CDDO-Me administration in healthy volunteers [69]. Subsequent Phase II trials have either been terminated or withdrawn. A CDDO-Me evaluation in patients with pulmonary hypertension is currently recruiting patients (clinicaltrials.gov NCT02036970). Clearly, CDDO usage in humans carries some kind of cardiovascular risk and the knowledge of autophagic sufficiency for CDDO efficacy in the cardiovascular system may provide a critical insight on targeting upstream regulators of both Nrf2 and autophagy.

6.2 Kidney Disease

Another realm of intense research into CDDO and related compounds is in chronic kidney disease (CKD). Impacting almost 13 % of the US population, CKD is a reduction in estimated glomerular filtration rate (eGFR) along with albuminuria (protein in the urine) that eventually results in a need for renal replacement and sequelae such as anemia and metabolic bone disease [74]. In fact, cardiovascular complications from CKD anemia such as left ventricular hypertrophy due to maladaptation can affect the kidneys further, creating a vicious loop of escalating damage termed “cardiorenal

anemia syndrome" that drastically reduces patient long-term survivability by 30 % [74]. To ameliorate the multiple effects of CKD, CDDO in its multiple forms has been extensively tested in animals and clinical trials have been held in humans. In rats, CKD studies have shown improvement in the areas of ROS, inflammation, and fibrosis, with CDDO-TFEA and CDDO-Me [41, 75]. Liu et al. [76] have found CDDO-Im to protect kidneys from ischemic reperfusion injury, which models the damage of CKD, and this protection is entirely dependent on Nrf2 as Nrf2-knockout mice treated with CDDO-Im showed no improvement. Wu et al. [77] showed that CDDO was able to ameliorate lupus-induced nephritis by reduction in ERK, STAT3, and Nf-κB, resulting in decreased CD4 T cell activation. Shelton et al. [78] conducted an extensive proteomic and transcriptomic analysis of wild type and Nrf2 knockout mice treated with CDDO-Me and found that CDDO-Me via Nrf2 upregulation positively regulated proteins related to redox homeostasis and NADPH regulation. The authors also concluded that CDDO would be useful in countering xenobiotics (such as cisplatin or cyclosporin) that generate large amounts of nephrotoxic molecules as well as chronic kidney insults from heavy metals [78, 79]. This clearly points to CDDO's potential to protect the kidneys during chemotherapy which Aleksunes et al. [80] explored in mice, finding that CDDO-Im could protect from cisplatin-induced nephrotoxicity. On the structural level, Aminzadeh et al. [81] found that CDDO-TFEA could ameliorate damage due to the cardiorenal axis with restoration of endothelial function in CKD rat aortic rings as measured by acetylcholine-mediated relaxation response. Additionally, CKD-induced aortic upregulation of MCP-1 angiotensin II and NADPH oxidases was all ameliorated by CDDO-TFEA [81].

These animal studies serve to illustrate that CDDO compounds are of great value in renal protection against chronic diseases. Indeed, in a Phase I trial conducted by Hong et al. in 2012, 47 patients diagnosed with solid tumors and lymphomas were given CDDO-Me in microcrystalline form for 21 consecutive days out of a 28-day cycle, with multiple cycles and saw an increase in eGFR estimated at 26 % in all patients with a 33.9 % increase in the highest dosage [7]. Clearly, CDDO-Me improved kidney health that may have been ravaged by antineoplastics and other chemotherapeutics. A Reata Pharmaceuticals-funded Phase II trial from 2008 to 2009 (clincaltrials.gov NCT00811889) found significant improvement in eGFR in patients treated with CDDO-Me at 24 weeks, with up to 10.5 additional ml (per minute per 1.73 m^2 body surface area) in the 75 mg dosage range [82]. Another Phase II study in 2010 by Reata (clinicaltrials.gov NCT01053936) evaluating CDDO-Me in eGFR in type 2 diabetes as well as another study (clinicaltrials.gov NCT00664027) was completed with no published data. Unfortunately, after initial Phase II success, a Phase III trial in 2014 (clinicaltrials.gov NCT013516750) was terminated due to an increase in cardiovascular adverse events, even though eGFR, renal function, and body weight improved significantly [83] (Table 2).

Table 2 Human studies involving CDDO-Me

Disease	References
Type 2 diabetes/CKD	[12, 82, 83]
Solid tumors	[7]

Table 3 Oncogenic targets of CDDO compounds

Target	References
Akt	[39, 100]
P38/MAPK	[43]
FLIP/TRAIL	[44, 45]
p42	[85]
hTERT	[63, 94]
mTOR	[95, 100]
ICAM	[96]
PDP Polymerase	[96]
Nf-κB	[38, 42]
BRCA1	[102]
Bcl	[103]
Hsp90	[64]

6.3 AML

Leukemia, especially acute myeloid leukemia, is defined as an increase in myeloid cells within the bone marrow and a subsequent insufficiency of the hematopoietic cells due to their failure to mature [84]. Ito et al. [45] reported that human AML cells underwent caspase 8-mediated apoptosis when treated with CDDO. Subsequent reports found that CDDO-Me could induce apoptosis in acute myelogenous leukemia, suppress MAPK in these cells, increase TRAIL sensitization, downregulate FLIP, promote hematopoietic progenitor expansion, and upregulate p42 CCAAT enhancer-binding protein alpha in granulocytes [43, 44, 85–87]. Although not yet used in human clinical trials, CDDO compounds show a clear effect in promoting aberrant leukocytes to undergo apoptosis while pushing differentiation/maturation of immature cells forward (Table 3).

6.4 Retinal Blindness

Damage to the eyes of diabetic patients is a well-known diabetic complication. Age-related macular degeneration due to oxidative damage may also be a concern in a rapidly aging population. A cytoprotective effect of CDDO-TFEA, CDDO-Im, and CDDO-Me was seen in retinal cell lines to protect against oxidation-induced retinal degeneration and the lipid phosphatase PTEN was inhibited in mice treated with CDDO-TFEA [59]. Wei et al. [88] found that Nrf2 protects both neurons and capillaries from retinal ischemia-reperfusion injury so the action of CDDO is protective to the retina via upregulation of Nrf2. Xu et al. [89] verified this in a separate report, showing that Nrf2 knockout mice experienced a greater loss of retinal neuron function. Other reports verified that Nrf2 can modulate cigarette smoke-induced complement activation in the retina and that Nrf2 is a critical

modulator of oxidation-induced death in the retinal ganglion [90, 91]. Experiments in astrocytes, microglia, and neurons showed that all CDDO compounds are protective against oxidative damage and upregulate antioxidant genes via Nrf2 [92]. Taken together, these results show that CDDO may hold promise for protecting the brain from age-related oxidative stress as well as treating such chronic eye diseases as macular degeneration and tobacco smoke-induced injury.

6.5 Cancer

CDDO compounds have been rigorously tested in multiple rodent cancer models, as its ability to force abnormal cells into apoptosis could form the basis of a chemotherapeutic approach that, unlike current xenobiotics and chemotherapeutics, also simultaneously protects the liver and kidneys. CDDO-Me has been used in colitis-associated colon cancer models in mice to interrupt inflammation-driven downregulation of prostaglandin dehydrogenase as well as the entire suite of inflammatory cytokines such as IL-6, iNOS, IL-1β, and TNFα [93]. A study by Alabran et al. that used CDDO compounds against multiple human neuroblastoma cell lines found that these cells underwent rapid arrest in S-phase, Bax was activated (apoptosis induction), and that CDDO compounds were effective against these cells in low concentrations (IC_{50} 5–170 nM) [9]. CDDO-Me has also been found to downregulate telomerase activity (hTERT) and induce cell death in pancreatic cancer cell lines [94]. However, it is unclear as to whether this hTERT inhibition is a direct interaction or an Nrf2-associated effect. A review by Shanmugam et al. details oleanolic acid derivatives and the genes they primarily affect, such as mTOR, AKT, STAT3, ICAM1, and PADP polymerase—all of which are critical for regulating cellular homeostasis and which may be compromised in transformed cells [95, 96]. As cancer cells use vascular endothelial growth factor (VEGF)-driven angiogenesis to form new capillary feeder networks, it is interesting to note that CDDO-Me has been reported in mice to suppress Matrigel plug angiogenesis in picomolar concentrations [18]. Coupled with induced arrest and apoptosis, a one-two punch of cutting off the blood supply and then inducing tumor cell death is an attractive prospect for a chemotherapeutic drug. It is important to note that CDDO compounds may harm cancerous cells but it must be remembered that normal cells are protected against insult [97]. Again, this may be due to a need for autophagic competency to accompany increased Nrf2 levels in order to be protected or in the mitochondrial Lon protease system, which is inhibited by CDDO [57]. In a rat liver cancer model involving aflatoxin, CDDO-Im proved a powerful and complete protection, with damage almost completely ablated by treatment [98]. Liby et al. [99] found that CDDO-Me and CDDO-ethyl amide could protect A/J mice against vinyl carbamate-induced lung cancer. This proves that CDDO compounds may be a powerful prophylactic against specific types of environmental carcinogens that transform cells by ROS damage.

Table 4 Anticancer mechanisms in cell lines treated with CDDO

Cell types	Cell lines	Mechanism	References
Human neuroblastoma	NB1691, 15 N, LAN-1, SK-N-AS	Apoptosis	[9]
Pancreatic cancer	MiaPaCa2, Panc-1	hTERT	[94]
Kaposi's sarcoma	KS-IMM	Angiogenesis	[18]
Ovarian cancer	CNCaP, PC-3, OVCAR-3, OVCAR-5, SK-OV3, MDAH-2774	Akt, Nf-κB, PPARγ	[39, 100]
Ovarian cancer	H08910	Hsp90	[64]
Esophageal squamous	Ec109, KYSE70, Het1A	Apoptosis and autophagy	[36]
Human breast cancer	SUM159, MDA-MB-231	Stem cell signaling	[104]
Breast cancer and macrophage-like	MCF-7, MDA-MB-231, RAW264.7	Apoptosis and autophagy	[60, 61, 104]

Not only can CDDO protect against somatic cancers but increasing evidence shows that it is effective against gender-specific cancers, as well. Interestingly, a report by Gao et al. revealed that CDDO-Me controls apoptosis in ovarian cancer by inhibiting AKT, NF-κB, and mTOR signaling without affecting PDK1 kinase or PP2A activity [39, 100]. Mammary carcinogenesis in polyoma middle T mice was slowed by CDDO-Me, extending lifespan by roughly 5 weeks, and BRCA1-mediated cancers in mice are delayed by CDDO-Me, as well [101, 102]. In prostate cancer, CDDO-Me regulates Bcl and other survival signals in TRAMP mice and hTERT can also be targeted by CDDO-Me in prostate cancer [63, 103]. There is also evidence that Hsp90 might be targeted by CDDO-Me in cancer cells [64].

There is a recent theory of cancer stem cells, which are cells from a tumor that possess stem cell abilities to differentiate into different cancer types. Current reports show that CDDO-Me can suppress stemness in esophageal cancer lines and triple negative breast cancer cells [36, 104].

Other oleanolic acid derivatives, such as SZC017, CDDO-2P-Im, CDDO-3P-Im, and HIMOXOL, are being evaluated for anticancer effects such as apoptotic induction ability and cancer cell arrest [60, 61, 105]. Also, vehicles for efficient delivery of CDDO by nanoparticles have been explored [106] (Table 4).

There have been several clinical trials for cancer treatment using CDDO-Me. Hong et al. accomplished a Phase I trial which showed promise in hepatoprotection but did not show significant improvement in tumor size as seen in animal models [7]. However, two Phase II studies in patients with advanced solid tumors (clinicaltrials.gov NCT00508807, NCT00529438) were completed but results were not disclosed. Although in vitro and animal models show great promise in using CDDO compounds as cancer treatments, a lack of published data in the two completed clinical trials makes it difficult to evaluate CDDO as a promising chemotherapeutic.

6.6 Liver

The liver is the most critical organ in the body for metabolic processes and detoxification by the cytochrome enzymatic pathways. This makes it susceptible to not just ROS damage but other hepatotoxic molecules that may be generated by medicines, chemical compounds, or alcohols. Shah et al. [107] found that CDDO-Im could protect HepG2 cells against acrolein-induced toxicity by GSH upregulation as well as reducing levels of death markers such as protein carbonyls. A report by Liu as far back as 1993 established that oleanolic acid could rescue large-dosage acetaminophen liver damage in mice and upregulate GSH levels [1]. This led to the logical conclusion that oleanolic acid derivates with even higher Nrf2 stimulating activity could protect the liver even better. As such, CDDO-dhTFEA was reported to induce hepatoprotective genes including thioredoxin reductase (Txnrd), glutamate cysteine ligase catalytic and modifier subunits (Gclc and Gclm), gamma-glutamyl transpeptidase 1 (Ggt1), heme oxygenase-1 (Ho-1), and NAD(P)H quinone oxidoreductase 1 (Nqo1), while also increasing bile flow in rats, as bile is related to GSH levels [108]. A review by Klaassen collates over 15 separate studies in rats and mice where hepatotoxic compounds such as acetaminophen, concavalin A, and high-fat diets saw their damage ameliorated by CDDO-Im or oleanolic acid [26]. This clearly indicates that Nrf2 is strongly hepatoprotective, especially against hepatic damage induced by medications for chronic diseases (e.g., large doses of acetaminophen for arthritis) or metabolic syndrome. Also of note in the Klaassen review is a summary of 6 Nrf2 knockout rodent models for use in studying liver disease and CDDO treatment, such as carbon tetrachloride and arsenic [26]. A comprehensive proteomic report by Walsh et al. [109] has found that CDDO-Me in mice induces cytochrome P4502A5, glutathione-S-transferase, UDP-glucose-6-dehydrogenase, and epoxide hydrolase, prompting the liver to begin detoxification with P450 enzymes while simultaneously protecting from subsequent free radical activity by inducing antioxidant response enzymes. Most importantly, they found that 97 % of the proteins induced by CDDO-Me were specific for Nrf2 signaling, reassuring researchers that non-Nrf2-targeting effects during treatment would be kept to a minimum [78]. As seen in other organs, CDDO compounds provide strong hepatoprotective abilities that may be useful in combatting damage from medications, environmental chronic exposure, and metabolic syndrome.

6.7 Sepsis/Sickle Cell/Lupus

The presence of lipopolysaccharides (LPS) in the bloodstream may produce an aggressive immune response including inflammation. LPS, along with active bacteria, may also induce a massive cytokine release, dilating the capillary network, and causing a severe and often fatal drop in blood pressure. This septic shock is often fatal. Noel et al. [110] explored ex vivo Nrf2 activation by CDDO-Me administration to monocytes obtained from human patients with septic shock. Their

results showed a differential activation between purified and peripheral monocytes, with purified monocytes decreasing in IL-6 production and peripheral monocytes increasing IL-6 production [110]. Another study using neutrophils and peripheral monocytes showed strong activation of antioxidant response and attenuation of inflammatory cytokine response (TNFα,MLP, etc.) upon treatment with CDDO-Im and CDDO-Me, revealing that Nrf2 activation may be protective against challenge with LPS [111]. An interesting report by Keleku-Lukwete et al. [112] showed that Nrf2 could modulate the clearance of plasma heme in a mouse sickle cell model with administration of CDDO-Im relieving organ inflammation and failure in the model mice. These studies indicate that CDDO can be useful in sepsis as well as in chronic inflammatory diseases such as sickle cell anemia.

7 Conclusion

Oleanolic acid has been used in China as traditional medicine for liver problems and can be found in many plants and foods [113]. Having shown promise in multiple organ systems, CDDO compounds (by virtue of the ability to strongly upregulate Nrf2) seemed set to serve as a panacea for chronic diseases. In the liver, kidneys, retina, blood, and bone marrow, CDDO works to upregulate Nrf2, which is highly protective against oxidative damage and also to modulate a host of signaling pathways, including Akt/PI3 K, mTOR, FLIP/TRAIL, and Myc. CDDO-mediated upregulation of Nrf2 in these organs and in cancer cell lines and animal models induces apoptosis of aberrant cells and protects normal cells against insult from both oxidative stress and environmental insult.

Unfortunately, CDDO has not shown promise in the amelioration of cardiovascular disease or human cancers. Although in vitro and in vivo animal studies have shown excellent results, systemic effects of CDDO have not been fully elucidated and, in human clinical trials, CDDO has actually shown deleterious effects in the heart. Although multiple studies have shown that, at least early on in heart disease, Nrf2 upregulation is cardioprotective, a seminal finding in mice has shown very strong evidence that a lack of Nrf2 response in later stage heart disease is actually protective [51, 114, 115]. Recent literature has dubbed this effect as “reductive stress” (RS) as opposed to “oxidative stress” (OS) and that too many antioxidants can actually cause damage to the tissue as they reduce (donate electrons to reduce charge as opposed to steal them and add charge) [116]. DNA, with a negatively charged backbone, could be easily damaged by reductive attack, damaging it repair. Clinical reports are filtering in that finding reductive stress can occur in post-surgical complications such as restenosis of balloon angioplasty and stenting (BAS) and post-exercise [117, 118]. Additionally, in cancer, high antioxidant responses may be protective to the cancer cells against ROS-inducing chemotherapy as well as ROS generated by their much higher basal metabolic rate. Nrf2 can also cause upregulation of genes that metabolize chemotherapeutics as well as upregulate the pentose phosphate pathway, increasing tumor cell proliferation and survival [28, 52, 53, 78].

Intriguingly, recent reports have found that the functional integrity of autophagy is needed to reap positive benefits from Nrf2 regulation, with upregulation of Nrf2 and autophagic dysfunction associated with negative outcomes [119]. It may be that Nrf2 upregulation can increase scavenging of free radicals but can also damage cells by reductive stress from which they cannot recover without autophagy to recycle reduced membrane or other cell components. In fact, since some antioxidants can be more damaging than free radicals (e.g., ECGC as reported by Lu et al.), it is entirely possible that a lack of autophagy is a necrotic death sentence for a reductively damaged cell [120]. In this case, it would be critical to regulate both Nrf2 and autophagy simultaneously by regulating a common upstream element. The deubiquitinase CYLD is a master key in the NF-κB pathway regulating inflammation and immune development, but has been shown to affect many other pathways such as TLR-mediated signaling, Wnt/Catenin, and Snail [121]. CYLD has been recently shown in a seminal report to regulate Nrf2 transcriptionally, repressing it via downregulation of the p38 MAPK/ERK pathway [122]. If CYLD could also be shown to negatively regulate autophagy, then it would be possible to downregulate CYLD locally in the heart and preserve autophagic function along with Nrf2 activation which would be the best of both worlds. Since there are critical autophagic components, such as p62 and HDAC6, that are K63 polyubiquitinated, it may be possible that CYLD can control autophagy by enzymatic action on p62 or some other component of the pathway [123, 124]. In conclusion, CDDO holds some promise for certain types of chronic diseases, but cardiovascular and cancer therapies might benefit if master upstream elements like CYLD could be exploited to control both Nrf2 and autophagic mechanisms to prevent damage from reductive stress.

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