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Mapping oxylipin signatures in human diseases using LC-MS/MS

Larissa R. Diniz [1], Rosangela S. Santos [1], Hector Oreliana [1], Ana Clara A. Zucão, Megumi N. Yukuyama, Guilherme R.S. Resende, Thais Satie Iijima, Lucas G. Viviani, Sayuri Miyamoto [*]

Departamento de Bioquímica, Instituto de Química, Universidade de São Paulo, São Paulo, Brazil

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ABSTRACT

Oxylipins, a diverse family of oxidized lipids derived from mono- and polyunsaturated fatty acids, are increasingly recognized as key mediators in redox biology and inflammation. They are produced through enzymatic pathways involving cyclooxygenases (COX), lipoxygenases (LOX), cytochrome P450s (CYP), and soluble epoxide hydrolase (sEH), as well as through non-enzymatic mechanisms including singlet oxygen and free radical-mediated lipid peroxidation. Advances in mass spectrometry, particularly targeted LC-MS/MS approaches, have enabled sensitive and selective quantification of oxylipins in complex biological matrices. This article provides a focused overview of oxylipin alterations in neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis), obesity, infectious diseases, chronic pain conditions, and inflammatory skin disorders.

1. Introduction to oxylipins

Oxylipins comprise a broad class of bioactive lipid mediators generated through the oxygenation of polyunsaturated fatty acids. In recent years, the term "oxylipin" has gained prominence as a unifying descriptor across various biological and biomedical disciplines. To examine how the usage of this terminology has evolved, we performed a bibliometric network analysis of publications indexed in PubMed using the keyword "oxylipin" (≥10 co-occurrences), visualized with VOSviewer (Supplementary Fig. S1). Interestingly, the resulting network reveals the chronological and thematic expansion of the term. Early publications are predominantly associated with molecular biology and gene regulation, whereas subsequent clusters emphasize plant biology and signaling molecules such as jasmonic acid. More recent literature shows a clear shift toward biomedical research, with keywords linked to oxidative stress, cardiovascular diseases, obesity, and metabolism. This transition highlights the growing impact of oxylipins on human health and disease.

Considering the growing recognition of oxylipins as key mediators in redox biology and inflammation, the following sections provide an overview of the basic enzymatic and non-enzymatic pathways involved in oxylipin formation, discuss their biological significance, and highlight how mass spectrometry-based profiling has advanced the investigation of oxylipins in neurodegenerative, metabolic, infectious, pain-related, and skin conditions.

2. Basic mechanisms of oxylipin generation

Oxylipins comprise a structurally diverse family of oxygenated lipids derived from mono- and polyunsaturated fatty acids (PUFA), including octadecanoids (18-carbon), eicosanoids (20-carbon), and docosanoids (22-carbon). The major PUFAs involved in oxylipin generation include linoleic acid (LA, 18:2, n-6), α-linolenic acid (ALA, 18:3, n-3), dihomo-γ-linolenic acid (DGLA, 20:3, n-6), arachidonic acid (AA, 20:4, n-6), eicosapentaenoic acid (EPA, 20:5, n-3), and docosahexaenoic acid (DHA, 22:6, n-3), all of which can undergo oxidation via enzymatic and non-enzymatic mechanisms. Fig. 1 shows selected oxylipins from the reviewed studies, highlighting their biosynthetic pathways. Abbreviations for all oxylipin mentioned in this article are listed in Table S6.

For comprehensive overviews of oxylipin biosynthetic pathways, the reader is referred to reviews by Refs. [1–3]. Briefly, enzymatic oxidation involves three main pathways: cyclooxygenases (COX), lipoxygenases

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* Corresponding author.
E-mail address: miyamoto@iq.usp.br (S. Miyamoto).

[1] Equal contribution.

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(LOX), and cytochrome P450 monooxygenases (CYP). COX enzymes convert arachidonic acid into prostanoids. LOX enzymes catalyze the regio- and stereospecific formation of hydroperoxides that are subsequently converted to mono- and poly-hydroxylated derivatives (HETEs and lipoxins). CYP enzymes, often in combination with soluble epoxide hydrolases (sEH), produce epoxy- and hydroxy-fatty acids. Among oxylipins, eicosanoids are the most extensively studied subclass.

Eicosanoid biosynthesis typically begins with the release of arachidonic acid (AA) from membrane phospholipids by cytosolic phospholipase A_2 (cPLA$_2$). The liberated AA is then metabolized by COX-1 or COX-2 into prostaglandin H_2 (PGH$_2$), a common precursor of prostaglandins (PGE$_2$, PGD$_2$, PGF$_2\alpha$), prostacyclin (PGI$_2$), and thromboxane A2 (TXA$_2$). Alternatively, LOX-mediated metabolism produces HpETEs (hydroperoxyeicosatetraenoic acids) and subsequently HETEs (hydroxyeicosatetraenoic acids), leukotrienes, and lipoxins [2]. CYP enzymes generate both mid-chain and ω-terminal HETEs, as well as epoxyeicosatrienoic acids (EETs) such as 14,15-, 11,12-, 8,9-, and 5,6-EETs, each formed as *R,S-* or *S,R-* enantiomers [4,5].

Non-enzymatic oxidation occurs via radical and non-radical species, leading to the formation of hydroperoxy-, hydroxy-, epoxy-, and keto-derivatives, as well as cyclic derivatives such as isoprostanes and neuroprostanes [6,7]. The mechanism of free radical-mediated lipid peroxidation (LPO) has been extensively studied [8]. This process begins with hydrogen atom abstraction from bis-allylic carbons in PUFAs, forming carbon-centered lipid radicals, which rapidly reacts with molecular oxygen to generate peroxyl radicals. These peroxyl radicals act as LPO propagators by further promoting hydrogen-abstraction, generating hydroperoxides and new lipid radicals. Lipids are also oxidized by non-radical reactive species such as singlet molecular oxygen. This reactive species oxidizes unsaturated lipids via *ene*-addition, yielding hydroperoxides with distinct regioselectivity [9]. For example, while free radical oxidation of linoleic acid produces hydroperoxides (HpODEs) at 9- and 13-positions, singlet oxygen uniquely generates 10- and 12-regioisomers, in addition to 9- and 13-HpODE [10].

3. Oxylipin biological significance

Oxylipins exert a wide range of biological effects by interacting with specific receptors, including nuclear receptors (e.g., PPARs), G-protein-coupled receptors (GPCRs), and ion channels, thereby influencing inflammation, vascular tone, immune function, blood pressure, renal physiology, and energy metabolism [11,12]. However, oxylipin signaling is highly complex due to their structural diversity, the existence of multiple biosynthetic pathways, and interactions with diverse receptor classes, many of which exhibit considerable ligand promiscuity [12]. Nevertheless, oxylipins play pivotal roles in the initiation, modulation, and resolution of inflammation, acting as either pro- or anti-inflammatory mediators depending on their chemical structure and receptor context.

Oxylipins have been widely detected in several biological samples, including urine, blood, and cerebrospinal fluid. While free (unesterified) oxylipins are generally considered biologically active, the majority of circulating oxylipins (>90 %) exist in esterified forms within phospholipids, triacylglycerols, or cholesterol esters in blood plasma [13]. Moreover, studies have demonstrated that exogenously added free oxylipins (e.g., HETEs) can be esterified into membrane phospholipids [14]. Alternatively, they can also be generated directly by the enzymatic and non-enzymatic oxidation of membrane lipids. The physiological relevance of these esterified pools is still under investigation but may include roles in signaling, or acting as reservoir for oxylipin regulated release.

In parallel, the metabolism of free oxylipins has emerged as a key determinant of their biological activity and temporal dynamics (Fig. 2). For example, mitochondrial β-oxidation is a major intracellular route for

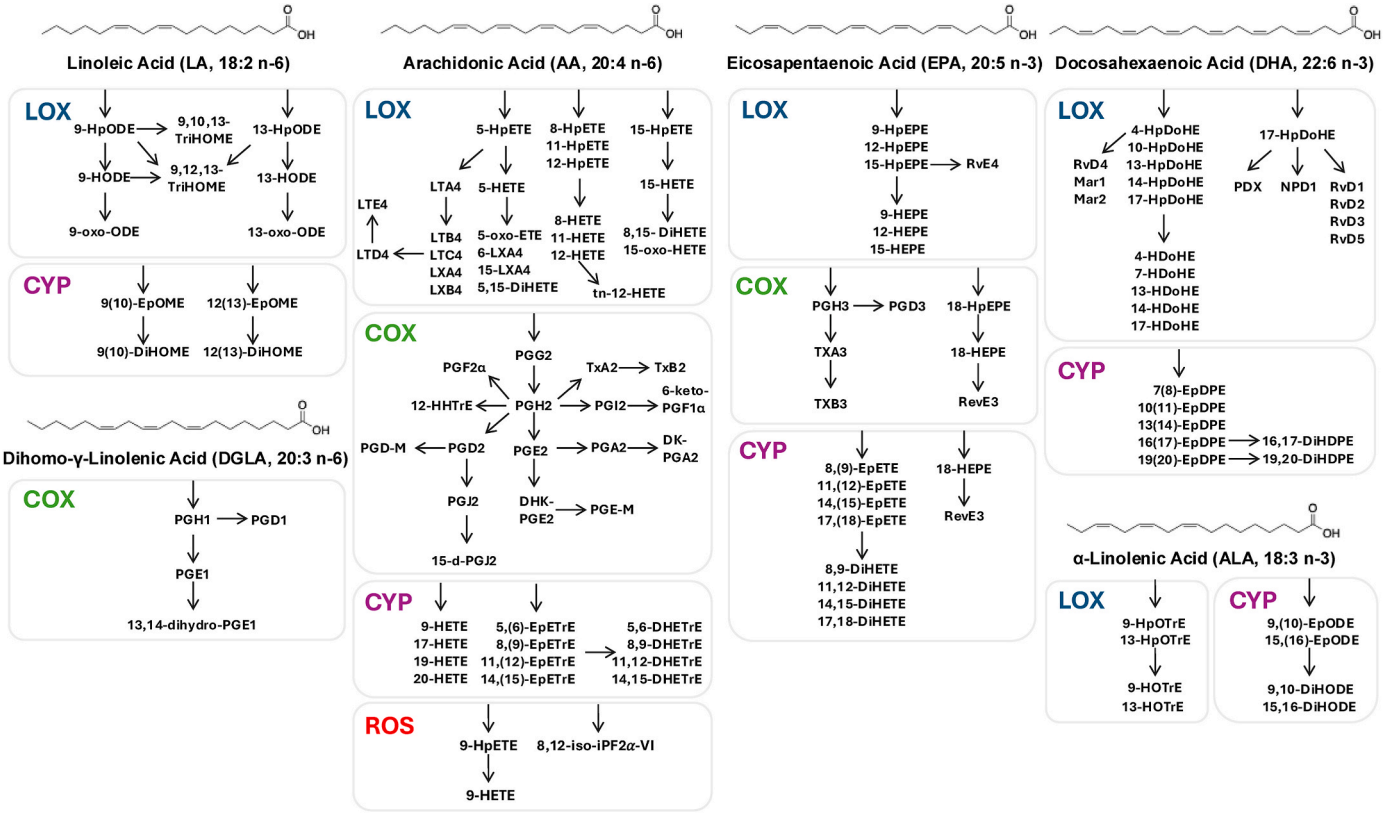

Fig. 1. Oxylipins detected in diseases, grouped by precursor fatty acid. The chemical structure of each precursor fatty acid is shown above the corresponding box. The first arrows within each box indicate the initial oxidation pathway catalyzed by lipoxygenase (LOX, blue), cyclooxygenase (COX, green), cytochrome P450 (CYP, violet), or by non-enzymatic oxidation via reactive oxygen species (ROS, orange). Secondary arrows represent subsequent conversions (e.g., epoxide → diol).

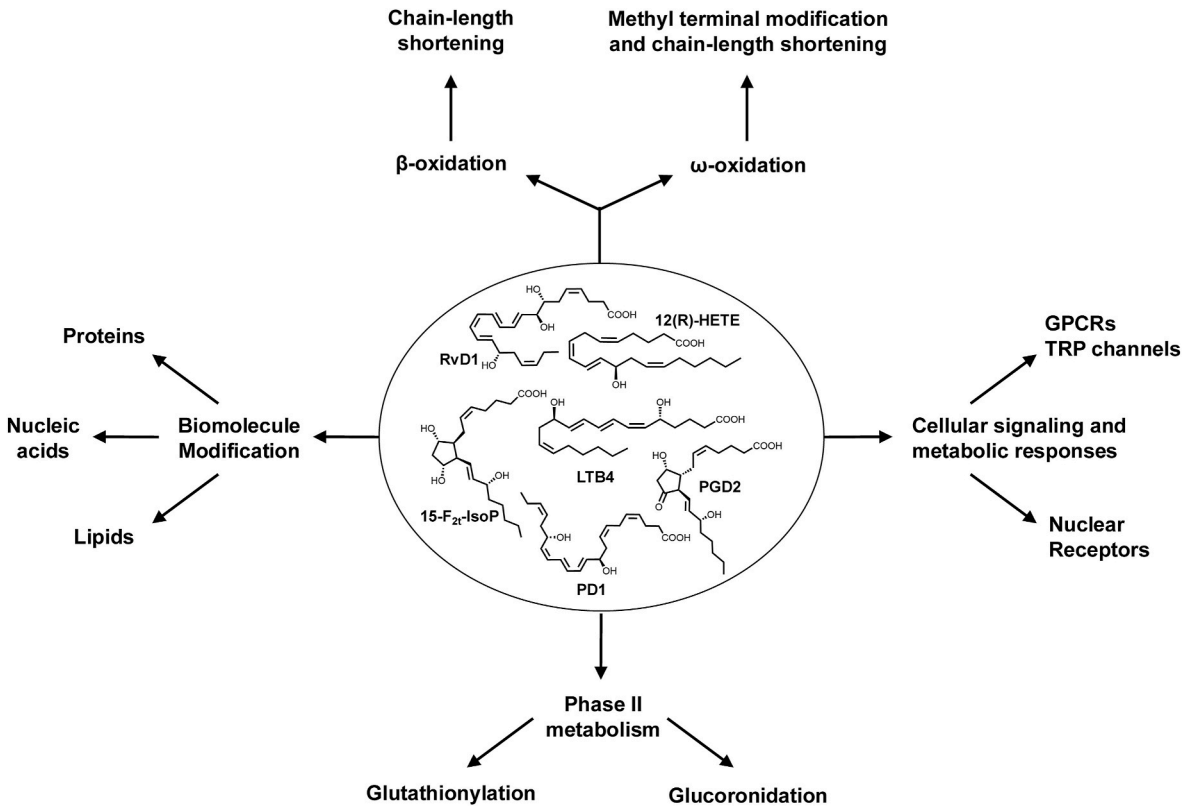

Fig. 2. Overview of pathways that affects oxylipin steady-state concentrations. Oxylipins are metabolized through distinct pathways responsible for their clearance, including mitochondrial β-oxidation (chain-length shortening), ω-oxidation (methyl-terminal modification and shortening), and Phase II metabolism (e.g., glutathione conjugation and glucuronidation). Additionally, electrophilic oxylipins can modify biomolecules such as proteins, nucleic acids (e.g., Michael-addition of 15d-PGJ_2), impacting their biological functions. Representative structures of oxylipins (RvD1, PD1, PGD2, 12-HETE, 15-F_{2t}-IsoP) are illustrated at the center of the figure. Oxylipins mediate cellular signaling and metabolic alterations by interacting with receptors, including G-protein coupled receptors (GPCRs), peroxisome proliferator-activated receptors (PPARs), transient receptor potential (TRP) channels, and other intracellular signaling pathways.

oxylipin clearance during inflammation [15]. Using stable isotope-labeled 12-HETE, Misheva et al. [15] traced its conversion into chain-shortened tetranor metabolites via sequential cycles of mitochondrial β-oxidation. Interestingly, inhibition of carnitine palmitoyltransferase 1 (CPT1), the rate-limiting enzyme for mitochondrial fatty acid import, led to significant accumulation of 12-HETE and its downstream derivatives, indicating that β-oxidation is essential for clearing this lipid mediator. These findings highlight mitochondrial metabolism as a critical regulator of oxylipin signaling and inflammation modulation.

Furthermore, oxylipins, including prostaglandins, leukotrienes, and resolvins, are rapidly metabolized through classical Phase I and Phase II pathways (Fig. 2), where they may compete for metabolic enzymes, potentially altering their activity or being differentially metabolized within these routes. Specialized Pro-resolving Mediators (SPMs) have been shown to undergo β-oxidation, ω-oxidation, and glutathione conjugation [16]. Additionally, oxylipins including LTB_4, 20-HETE, F_2-isoprostanes, and Resolvins D5 and D1 are readily metabolized to glucuronide conjugates [17–21]. Therefore, despite analytical challenges, it is crucial that future studies further characterize both oxylipins and their downstream metabolites to gain deeper insight into their metabolic fate and functional roles.

4. Analytical approaches to oxylipin quantification

Over the past two decades, oxylipin analysis has advanced considerably, driven by improvements in analytical sensitivity, specificity, and reproducibility. Modern mass spectrometry platforms, particularly liquid chromatography-tandem mass spectrometry (LC-MS/MS), now enable the simultaneous quantification of over 100 oxylipin species from small volumes of biofluids or tissue extracts, with detection limits in the low-to sub-picogram range (on-column) in a single analytical run. These capabilities make the method suitable for profiling endogenous oxylipins, even in samples with limited availability or high metabolic turnover.

Despite these advances, oxylipin quantification remains technically challenging. Oxylipins are present at low nanomolar to picomolar concentrations, are subject to rapid enzymatic and non-enzymatic metabolism, and exhibit considerable structural diversity, including numerous regio- and stereoisomers. In addition, their susceptibility to *ex vivo* degradation, oxidation, and isomerization requires careful sample handling and optimized extraction protocols. Accurate quantification thus relies on a combination of robust chromatographic separation (e.g., UHPLC), high-resolution detection (e.g., Q-TOF or Orbitrap) or tandem mass spectrometry (MS/MS), and the use of authentic and isotopically labeled internal standards to control for matrix effects, ion suppression, and analyte recovery.

Importantly, analytical workflows should be carefully optimized for each oxylipin subclass, as differences in polarity, chemical stability, and functional group composition can markedly influence extraction efficiency, chromatographic retention, and fragmentation behavior across lipid classes. To enhance reproducibility and cross-laboratory comparability, both essential for mechanistic and translational studies, an oxylipin working group within the International Lipidomics Society (ILS, https://lipidomicssociety.org/interest_groups/oxylipin-analysis/) has issued guidelines for oxylipin analysis and reporting [22]. These community-driven standards outline best practices for method validation, quantification criteria, and essential metadata reporting, aiming to

improve inter-laboratory consistency and facilitate standardized interpretation of oxylipin profiles in biological and clinical studies.

In the present review, all articles were selected based on the criteria established in the guideline. Only studies employing LC-MS platforms with isotopically labeled internal standards were included, with preference given to those that performed comprehensive oxylipin profiling. The complete list of references analyzed, along with detailed information on LC-MS methods (including instrumentation and internal standards), is provided in Table S1–S5. For each selected study, we described the oxylipins reported as increased or decreased, and this information was consolidated across the five disease categories in Table S7 and Fig. 3. In the following sections, we highlight key oxylipin alterations reported in neurodegenerative, metabolic, infectious, pain-related, and skin diseases.

5. Oxylipins in neurodegenerative diseases

Neurodegenerative diseases are characterized by progressive neuronal dysfunction and cell death, often involving oxidative stress and lipid peroxidation as central pathophysiological features. Although research on oxylipins in neurodegenerative diseases is still emerging, several studies have begun to map oxylipin profiles in conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS), and Amyotrophic Lateral Sclerosis (ALS) (Table 1).

5.1. Alzheimer's disease (AD)

Analysis of oxylipins in the blood plasma of AD and mild cognitive impairment (MCI) patients revealed a significant increase in metabolites from the cytochrome P450-soluble epoxide hydrolase (CYP-sEH) pathway, including diols from AA (DiHETrEs), and EPA (17,18-DiHETE), along with an epoxide from LA (9,10-EpOME) [23,24,27].

Similarly, oxylipins analysis of cerebrospinal fluid (CSF) from AD patients showed elevated levels of LA-derived epoxide 9,10-EpOME and a moderate increase in its corresponding diols, without a marked accumulation of CYP-sEH metabolites derived from longer-chain PUFA [23]. These findings are consistent with previous reports of increased sEH expression in post-mortem AD brains [38] and in astrocytes from APP/PS1 transgenic mice [39]. Notably, pharmacological inhibition of sEH reversed microglial and astrocyte reactivity and ameliorated cognitive deficits in AD models [38]. Furthermore, in a CSF lipid mediator study involving a cohort of AD, MCI, and subjective cognitive impairment (SCI) patients, several DHA-derived products (RvD4, RvD1, NPD1, MaR1) were found to be reduced in AD and/or MCI compared to SCI patients. In contrast, levels of the pro-inflammatory LTB_4 and 15-HETE, derived from COX and 15-LOX pathways, were elevated in AD and MCI [26].

Additionally, a complementary study analyzing human AD brains identified oxylipins that correlated either positively or negatively with clinical phenotypes [25]. Metabolites showing positive correlations included CYP-sEH-derived products of AA and EPA (11,12-DHETrE, 5, 6-DHETrE, and 14,15-DiHETrE), LOX-derived species (12-HETE, 5-HETE, 5-KETE, and 9-HETE), and the COX-derived PGD_2. In contrast, several downstream or degradation products, including 11-dehydro-2, 3-dinor-TXB_2, 13,14-dihydro-15-keto-PGA_2, isoprostane 5(RS)-5-F_2t-IsoP, and the PGD_2 catabolite tetranor-PGJM were negatively associated with disease severity [23,24,27].

5.2. Parkinson's disease (PD)

Analysis of 158 oxidized fatty acid metabolites in blood plasma of PD patients revealed a significant elevation of 13-HOTrE, a 15-LOX-derived metabolite of α-linolenic acid (ALA), along with reduced levels of several key metabolites from the CYP-sEH pathway, including DiHETrEs (from AA), DiHOMEs (from LA), 17,18-DiHETE (from EPA), and the LOX product 12-HETE, derived from AA [37]. This reduction in CYP-sEH-derived products was somewhat unexpected, as prior studies have reported increased sEH expression in post-mortem brains of individuals with dementia with Lewy bodies [40].

In a separate study, oxylipin profiles were analyzed across different stages of Parkinson's disease (PD) to investigate their potential role in disease progression [36]. Comparative lipidomic analysis between early- and advanced-stage patients revealed distinct patterns of oxylipin regulation. In advanced-stage PD, there was a marked upregulation of pro-inflammatory lipid mediators. Notably, increased levels of AA metabolites such as 19-HETE, 12-HETE, PGD_2, and the combined PGA_2/PGJ_2 were observed, indicating enhanced activity of the LOX and COX pathways. In parallel, elevations in 8-HDoHE (from DHA), 9-KODE and 13-KODE (from LA), and circulating EPA were detected. Conversely, levels of anti-inflammatory and resolution-associated mediators, such as anandamide (AEA) and leukotriene E_4 (LTE_4) were reduced, indicating a chronic unresolved inflammatory state.

5.3. Multiple sclerosis (MS)

MS is a chronic autoimmune demyelinating disorder, with various clinical phenotypes distinguished by recurrence and progression: relapsing-remitting (RR), primary-progressive (PP), secondary-progressive (SP), progressive-relapsing (PR), and clinically isolated syndrome (CIS) [41]. Oxylipin LC-MS profiling of CSF from MS patients revealed alterations in both pro-inflammatory and pro-resolving mediators. LA-derived 9-HODE and 13-HODE were elevated in CIS and RR patients compared to healthy controls [31]. Another study analyzing CSF oxylipin detected increased levels of AA-derived PGE_2 and 15-HETE [32], suggesting activation of COX and 15-LOX pathways in the brain of highly active MS patientes compared to less active ones. These oxylipins were similarly found to be elevated by GC-MS in a study comparing 46 MS patients, 46 healthy siblings and 50 controls [42], further supporting their potential as prognostic markers in MS.

Oxylipin alterations were also observed in the blood plasma of MS patients, where both LOX-derived (12-HETE, 15-HETE) and COX-derived products (PGE_2, PGD_2, TXB_2) were elevated, alongside DHA-derived mediators (14-HDHA, 17-HDHA, RvD5, PDX). These increases were detected in RR and PR patients, with higher concentrations observed in PR group [35].

In postmortem brain tissue from MS patients, oxylipin profiling revealed elevated levels of esterified CYP-derived epoxides, including EpOMEs (from LA), EpETrE (from AA), and EpDPEs (from DHA). Notably, seven esterified pro-resolvin fatty acid epoxides within neutral lipids were significantly increased (by 126 %–285 %) in the prefrontal cortex of MS patients compared to controls. In contrast, no significant changes were observed in free or phospholipid-bound oxylipins, suggesting that lipid mediator alterations in MS may be compartmentalized within neutral lipid pools [34].

In the spinal cord from experimental autoimmune encephalomyelitis (EAE) mouse model of MS, targeted oxylipin analysis revealed a marked shift in eicosanoid metabolism favoring the PGE_2 pathway, accompanied by suppression of PGD_2, and 5-LOX-derived metabolites [33]. Levels of PGE_2 and its major tissue metabolite, DHK-PGE_2, were significantly elevated, making them the predominant eicosanoids in acute spinal cord lesions. Conversely, concentrations of PGD_2, 5-HETE, LTB_4, LTC_4, and LTD_4 were substantially reduced throughout disease progression, highlighting an imbalance between pro-inflammatory and pro-resolving lipid mediators. Notably, Sanchez-Fernandez et al. [43] reported that specialized pro-resolving mediators (SPMs) were undetectable or present only at trace levels in the spinal cord of EAE mice as well as in the CNS and periphery of MS patients and this was linked to impaired expression of the enzymes involved in their biosynthetic pathways. These findings underscore the ongoing controversy surrounding in vivo SPM detection [44]. Despite their recognized roles, SPMs are often difficult to quantify due to their low abundance, rapid turnover, and methodological variability. This reinforces the need for

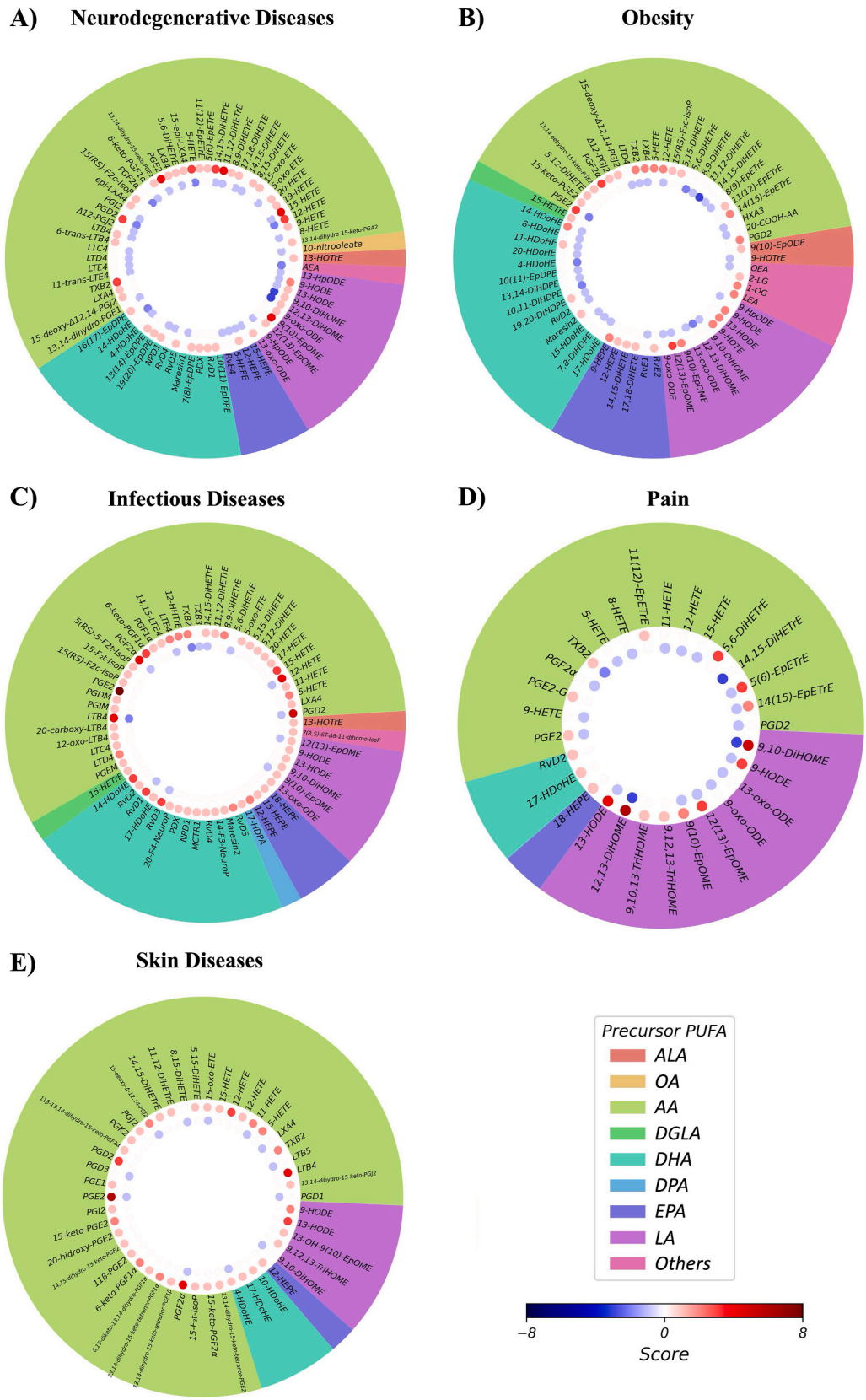

Fig. 3. Comparative overview of oxylipins detected by LC-MS/MS in A) Neurodegenerative diseases, B) Obesity, C) Infectious diseases, D) Pain, and E) Skin diseases. Oxylipins are displayed in a circular layout and grouped by precursor fatty acid (indicated by color). The inner dots represent the frequency with which each oxylipin was reported across the analyzed studies, with the color gradient indicating regulation status: blue = downregulated, red = upregulated, and intermediate shades reflecting mixed reports. Data for this figure were extracted from the systematic literature compilation summarized in Table S7. Plots were generated in Python with Matplotlib.

Table 1
Oxylipin species reported in selected publications on neurodegenerative diseases.

Disease	Population (illness/control)	Sample	Up-regulated	Down-regulated	N° of Oxylipin Monitored	Conc. Range	Ref.
Alzheimer's Disease	Human (150/135)	Blood Plasma	17,18-DiHETE; 9,10-EpOME; 11,12-DiHETrE; 14,15-DiHETrE	$PGF_2\alpha$; PGD_2; AEA; 8-HETE; 5-HEPE; 9-HEPE; 12-HEPE; 15-HEPE; 4-HDoHE; 14-HDoHE	85	0.1–20.1 nM	[23]
	Human (150/135)	Cerebrospinal Fluid (CSF)	9,10-DiHOME; 12,13-DiHOME; 9(10)-EpOME; 12(13)-EpOME	$PGF_2\alpha$; 14,15-DiHETE	85	0.1–20.1 nM	[23]
	Human (45/39)	Blood Serum	11,12-DiHETrE, 14,15-DiHETrE, 5,6-DiHETrE, 8,9-DiHETrE	10-nitrooleate	76	0.2–119 nM	[24]
	Human (6/6)	Post-mortem Brain	13,14-dihydro-15-keto-PGA_2; PGE_2-derived metabolites	11-trans-LTE_4; 5.6-DiHETrE-lactone; 15-HETE; 13,14-dihydro-PGE_1	193	Not Specified	[25]
Alzheimer Disease (AD); Mild Cognitive impairment (MCI); Subjective Cognitive Impairment (SCI)	Human (AD: 40, MCI: 43, SCI: 53)	Cerebrospinal Fluid (CSF)	*AD and MCI vs SCI:* LTB_4; 15-HETE	*AD and MCI vs SCI:* RvD4; NPD1; PGE_2 *MCI vs SCI:* MaR1; RvE4; PGD_2	18	0.13–57 (values are unitless)	[26]
Mild Cognitive Impairment (MCI)	Human (60/56)	Blood plasma	5-HETE, 9-HODE, 20-HETE, 11,12-DiHETrE, 14,15-DiHETrE, 9(10)-EpOME	12-HETE	49	0.16–31.6 nM	[27]
Amyotrophic Lateral Sclerosis (ALS)	Human (78/9)	Blood Plasma		9,10-DiHOME; 12,13-DiHOME; 13-HODE; 9-HODE; 5-HETE; 5-oxo-ETE; 14-HDoHE	50	0.0033-6,3 ng/mL	[28]
	SOD1*G93A rats (12/12)	Blood Plasma	6-trans-LTB_4; 5-HETE; 9-HETE; epi-LXA_4; 15-*epi*-LXA_4; 15-oxo-ETE; 8,15-DiHETE; 15(RS)-F_2c-IsoP; TXB2; PGD_2; 15-deoxy-$\Delta^{12,14}$-PGJ_2, 9-oxo-ODE; 13-oxo-ODE	9,10-DiHOME; 12,13-DiHOME	126	0.8–200 ng/mL	[29]
	SOD1*G93A mice (49/24)	Blood Plasma	5-HETE, 12-HETE, 15-HETE, PGE_2, PGD_2, TXB_2		23	0.5–30 pmol/mg protein	[30]
	SOD1*G93A mice (49/24)	Brain	12-HETE, 15-HETE		23	0.5–30 pmol/mg protein	[30]
Multiple Sclerosis	Human (41/22)	Cerebrospinal Fluid (CSF)	9-HODE, 13-HODE		37	0.1–9500 nM	[31]
	Human (20/0)	Cerebrospinal Fluid (CSF)	PGE_2, 15-HETE, RvD1		16	0.02–1500 pg/mL	[32]
	EAE mice (30/1)	Spinal Cord	13,14-dihydro-15-keto-PGE_2, PGE_2	5-HETE, LTB_4, LTD_4, LTC_4, PGJ_2, PGD_2, Δ^{12}-PGJ_2, 6-keto-$PGF_1\alpha$	14	0.02–20 ng/g of tissue	[33];
	Human (10/5)	Brain	9(10)-EpOME, 5(6)-EpETrE, 11(12)-EpETrE, 7(8)-EpDPE, 10(11)-EpDPE, 13(14)-EpDPE, 16(17)-EpDPE, 19(20)-EpDPE		72	5.0–8000 pmol/g	[34];
	Human (38/14)	Blood Plasma	PGE_2, PGD_2, TXB_2, 12-HEPE, LXA_4, LXB_4, RvD_5, PD1, PDX, 17-HDHA, 14-HDHA		38	0.01–600 pg/mL	[35]
Parkison's Disease	Human (73/36)	Blood Plasma	19-HETE, 12-HETE	AEA, LTE_4	Not Specified	Not Specified	[36]
	Human (42/54)	Blood Plasma	13-HOTrE	9-HpODE; 13-HpODE; 5,6-DiHETrE; 11,12-	158	Not Specified	[37]

(*continued on next page*)

Table 1 (*continued*)

Disease	Population (illness/control)	Sample	Up-regulated	Down-regulated	N° of Oxylipin Monitored	Conc. Range	Ref.
				DiHETrE; 14,15-DiHETrE; 12-HETE; 17,18-DiHETE; 9,10-DiHOME; 12,13-DiHOME			

more standardized and sensitive analytical approaches for lipid mediator research.

5.4. Amyotrophic lateral sclerosis (ALS)

Oxylipin profiling of blood plasma ALS patients with spinal or bulbar onset revealed decreased levels of LA-derived metabolites from the CYP-sEH pathway, specifically 9,10-DiHOME and 12,13-DiHOME [28]. Consistent with these findings, reduced DiHOME levels were also observed in the blood plasma of $SOD1^{G93A}$ ALS rat model [29]. DiHOMEs have been reported to enhance fatty acid uptake and mitochondrial β-oxidation in brown adipose tissue and skeletal muscle, particularly in response to cold exposure or exercise. Their reduction in ALS has been hypothesized to contribute to the hypermetabolic phenotype observed in this condition, particularly in muscle tissue, which is characterized by a shift in energy substrate from glucose to lipids.

Oxylipin analysis of blood plasma of ALS animal models also revealed elevated levels of multiple inflammation-associated oxylipins, including PGD_2, TXB_2, 6-trans-LTB_4, 5-HETE, 9-oxo-ODE, and 13-oxo-ODE [29]. Notably, the increase in PGD_2 in ALS animals mirrors findings in ALS patients showing elevated urinary levels of its stable tetranor metabolite, PGD-M [45], supporting its potential role as a biomarker for disease progression. Further studies with larger patient cohorts are warranted to confirm these observations.

5.5. Conclusion

Studies addressing the molecular mechanisms underlying oxylipin alterations in neurodegenerative diseases are still in their early stages. Current evidence, however, suggests a strong association between these disorders and disruptions in LOX-, COX- and the CYP-sEH-derived products. The graphic overview in Fig. 3 highlights that oxylipins most frequently reported in neurodegenerative diseases include prostaglandins (PGE_2, PGD_2, TXB2) and HETEs (12-HETE, 15-HETE), which are consistently upregulated across studies. While LA-derived metabolites (HODE and DiHOMEs) show both up- and down-regulation depending on the study. These recurrent findings support the idea that eicosanoid and octadecanoid imbalance is a central feature of neuroinflammation. In ALS, for example, LA-derived metabolites (9,10-DiHOME and 12,13-DiHOME) generated via CYP-sEH were markedly decreased in blood plasma from both patients and animal models [28,29]. In AD, increased sEH activity and reduced levels of its substrates have been reported in both human patients and animal models [38,46], consistent with the beneficial effects of both genetic [39] and pharmacological [38] inhibition of sEH in AD mouse models. Similar trends, albeit less extensively studied and sometimes contradictory, have also been reported in PD patients [40]. Despite these promising findings, further investigation is required to clarify the mechanistic roles of oxylipins generated by CYP-sEH axis in neurodegeneration.

6. Obesity

Obesity is a major risk factor for metabolic disorders including dyslipidemia, non-alcoholic fatty liver disease (NAFLD), atherosclerosis, hypertension, and insulin resistance, which can ultimately progress to type 2 diabetes (T2D). A central mechanism linking obesity to these pathologies is chronic low-grade inflammation, primarily driven by overnutrition. Sustained overfeeding leads to sustained elevations in insulin, leptin, and catecholamines, which stimulate adipocyte expansion and proliferation. Once adipose tissue reaches its storage threshold, metabolic stress ensues, triggering inflammatory signaling cascades and promoting immune cell infiltration [47].

Oxylipin profiling of blood plasma samples from severely obese individuals revealed significantly elevated levels of circulating saturated, monounsaturated, and polyunsaturated fatty acids, along with increased concentrations of specific bioactive lipid mediators, compared to healthy overweight or less severely obese counterparts [48] (Table 2). Notably, severely obese individuals exhibited higher levels of LOX-derived oxylipins, including 11-HDoHE and 14-HDoHE (from DHA), 12-HETE (from AA), and 12-HEPE (from EPA), indicating a metabolically altered oxylipin profile [48]. A similar increase in LOX-derived oxylipins was also observed mice fed a 60 % high-fat diet for 18 weeks, with elevation of 13-HODE and 9-HODE (from LA), 9-HOTE (from ALA), and 9-HEPE (from EPA) detected in both adipose tissue and liver [49]. Additionally, COX-derived prostaglandins including PGD_2, Δ^{12}-PGJ_2, and 15-deoxy-PGJ_2 were increased in adipose tissue, consistent with a high fat diet-induced pro-inflammatory lipid profile [49].

In young obese adults, plasma levels of omega-6-derived oxylipins, 15-HeTrE and 5-HETE (LOX products from AA), 14,15-EpETrE (CYP-derived epoxide of AA), and 15(RS)-F_2c-IsoP (a non-enzymatic F_2-isoprostane generated under oxidative stress), were positively correlated with adiposity, metabolic syndrome prevalence, fatty liver index, insulin resistance (HOMA-IR), and dyslipidemia [51]. In contrast, three omega-3-derived dihydroxy oxylipins formed by CYP-sHE pathway, 14,15-DiHETE and 17,18-DiHETE (from EPA), and 19,20-DiHDPE (from DHA), were negatively associated with these metabolic parameters [51].

Consistent with these findings, Hateley et al. [50,50] reported significant alteration in plasma oxylipins across lean individuals, obese individuals, and obese patients with Type 2 Diabetes Mellitus (T2DM). The diabetic group exhibited significantly reduced levels of omega-3-derived epoxides, including 10,11-EpDPA, 7,8-DiHDPA, and 19,20-DiHDPA, while showing elevated 12,13-EpOME:DiHOME ratio, suggesting an impaired CYP-sEH pathway function in obesity. In the same study, analysis of omental white adipose tissue (WAT) from obese individuals displayed a coordinated reduction of oxylipins derived from DHA, AA, and LA. Specifically, diols such as 10,11-DiHDPE (from DHA), multiple DiHETrEs (from ARA), and DiHOMEs (from LA), were significantly decreased, supporting the interpretation of reduced CYP-sEH activity in WAT. This was further supported by elevated EpOME:DiHOME and EpETrE:DiHETrE ratios, reflecting decreased soluble epoxide hydrolase (sEH) activity in WAT and liver, respectively [50]. Collectively, these alterations suggest impaired resolution of inflammation in WAT, as epoxides tend to exert anti-inflammatory and pro-resolving effects.

Grapov et al. [56,56] reported that obese diabetic women had elevated plasma levels of CYP-derived epoxides from AA, including 11(12)-EpETrE and 14(15)-EpETrE, together with their corresponding sEH-derived diols (11,12-DiHETrE and 14,15-DiHETrE). They also displayed high levels of epoxides derived from LA such as 9(10)-EpODE, 9(10)-EpOME, and 12(13)-EpOME, indicating defective CYP-sEH

Table 2
Oxylipin species reported in selected publications on obesity.

Disease	Population (illness/control)	Sample	Up-regulated	Down-regulated	N° of Oxylipin Monitored	Conc. Range	Ref.
Obesity	Human (63 obese/116 severe obese)	Blood Plasma	12-HETE, 11-HDoHE, 14-HDoHE, 12-HEPE		48	0.001–14.1 nM	[48]
	Human (50/9): lean patients (N = 9), patients with obesity (N = 50) and patients with obesity and T2DM (N = 25)	Blood Plasma	12(13)-EpOME:DiHOME (ratio)	10,11-DiHDPA, 5,6-DHET, 8,9-DHET, 11,12-DHET, 14,15-DHET, 12,(13)-EpOME, 9,10-DiHOME, 12,13-DiHOME	57	10–40000 pg/g	[50]
	Human (20/82) Young Adults	Blood Plasma (EDTA)	15-HETrE, 5-HETE, 14(15)-EpETrE, 15(RS)-F_2c-IsoP, 14,15-DiHETE, 17,18-DiHETE, 19,20-DiHDPE		83	5–600 nM	[51]
	Human (52/7) lean patients (N = 7), patients with obesity (N = 52) and patients with obesity and T2DM (N = 26)	Omental WAT	9(10)-EpOME:DiHOME (ratio), 12(13)-EpOME:DiHOME (ratio)	10,11-DiHDPE, 5,6-DiHETrE, 8,9-DiHETrE, 11,12-DiHETrE, 14,15-DiHETrE, 12 (13)-EpOME, 9,10-DiHOME, 12,13-DiHOME	57	10–100000 pg/g	[50]
	Human (6/-)	imWAT, sWAT, vWAT	*IMAT*: TXB_2, PGE_2, 5-HETE, 12-HETE		7	0.0005–0.005 ng/mg/hr	[52]
	Human (41/7)	Visceral Adipose Tissue	PGE_2, PGD_2, $PGF_2\alpha$, TXB_2, LXB_4, 5,15-DiHETE, 5,12-DiHETE		27	0.2–407.8 pg/ 400 mg tissue	[53]
	Human (45/39)	Subcutaneous White Adipose Tissue (scWAT)	$PGF_2\alpha$	9-HpODE, 9-oxo-ODE, 13-oxo-ODE, 12,13-DiHOME, 11,12-DiHETrE, LTD_4, LXB_4, HXA3, 20-COOH-AA, 9-HOTrE, 4-HDoHE, 8-HDoHE, 11-HDoHE, 14-HDoHE, 15-HDoHE, 17-HDoHE, 20-HDoHE, RvD2, RvE1	Not Specified	Not Specified	[54]
	Mice (8/8)	Adipose Tissue	13-HODE, 9-HOTE, 9-HEPE, 9-HODE, 1-OG, LEA, 2-LG, PGD_2, Δ^{12}-PGJ_2, 15-deoxy-$\Delta^{12,14}$-PGJ_2		Not Specified	2.5–150 pmol/g	[49]
	Mice (5/5)	BAT, Liver	14-HDoHE, Mar2		3	0.1–4500 pg/mg protein	[55]
Obesity/ T2 Diabetes	Human (12/43)	Blood Plasma (EDTA)	9(10)-EpODE, 9(10)-EpOME, 12(13)-EpOME, 11(12)-EpETrE, 14(15)-EpETrE, 11,12-DiHETrE, 14,15-DiHETrE, 13-oxo-ODE		40	0.07–15.2 nM	[56]
	Human (lean: 9, obese: 10, TD2: 11)	Blood Plasma	$PGF_2\alpha$, PGE_2, 15-keto-PGE_2, 13,14-dehydro-15-keto-PGE_2		13	Not Specified	[57]
	Mice (6/6)	eWAT	LXB_4, RvE_2	PGE_2, 4-HDoHE	33	0.01–100 pg/mg	[58]

pathway activity in obesity and T2DM.

Complementary evidence from Tans et al. [57,57] demonstrated that plasma levels of COX-derived prostaglandin, including $PGF_2\alpha$, PGE_2, 15-keto-PGE_2, and 13,14-dihydro-15-keto-PGE_2, were elevated in obese individuals with T2DM but not in BMI-matched obese individuals without diabetes. This indicates that upregulation of COX-derived oxylipins is more strongly associated to the diabetic state than to adiposity alone.

Taken together, as summarized in Fig. 3B, oxylipin profiling support a model in which obesity and T2DM are characterized by dysregulation

of CYP-sEH and COX pathways, marked by consistent upregulation of PGE_2, $PGF_2\alpha$, and 12,13-EpOME across the selected studies. In contrast, 11,12-DiHETrE, a CYP-derived diol with potential anti-inflammatory roles, was markedly downregulated.

7. Oxylipins in infectious diseases

Oxylipins are increasingly recognized as critical lipid mediators in infectious diseases caused by viral and bacterial pathogens, where they exert dual roles by orchestrating both pro-inflammatory and pro-resolution responses. Classical pro-inflammatory mediators such as prostaglandins (e.g., PGE_2) and leukotrienes (e.g., LTB_4) are frequently upregulated during infection and contribute to the initiation and amplification of host immune responses. In contrast, pro-resolving mediators are thought to be critical in promoting tissue repair and restoring homeostasis. However, during inflammation, it is common to observe simultaneous increases and decreases in both pro-inflammatory and pro-resolving mediators across different biological matrices, such as human plasma, serum, and bronchoalveolar lavage fluid [59–61]

In infectious diseases, as highlighted in Fig. 3C, the lipidomic signature is dominated by a strong upregulation of pro-inflammatory mediators, notably $PGF_2\alpha$, PGE_2, PGD_2, and LTB_4, reflecting an increased activation of the COX and 5-LOX pathways. PGE_2 was elevated in seven out of fourteen studies (Table 3), reinforcing its role in acute inflammation. TXB_2, a stable thromboxane A_2 metabolite, was also frequently increased in bronchoalveolar lavage and plasma samples from COVID-19 patients, reflecting enhanced platelet activation and vascular involvement [59,62,63]. Conversely, reduced levels of 9, 10-DiHOME and 5,6-DiHETrE were reported in patients with sepsis-associated acute kidney injury, where they were proposed as potential diagnostic biomarkers [64].

Despite some degree of concordance across studies, the identification of specific oxylipins as reliable biomarkers of infectious or inflammatory diseases remains challenging. A major limitation is the lack of methodological standardization, which hinders inter-laboratory comparisons and prevents the establishment of reference values for clinical applications. Variability in sample types, extraction protocols, LC-MS instrumentation, and particularly in the selection and reporting of internal standards (IS), significantly undermines cross-study reproducibility. Although IS are essential for accurate quantitative oxylipin analysis, five of the sixteen studies reviewed did not clearly specify the IS species or their concentrations (Table S3). Furthermore, factors such as the choice of anticoagulants and the use of serum instead of plasma can directly affect oxylipin measurements [72].

Encouragingly, some studies have set a benchmark for methodological transparency. In particular, Misheva et al. [15] and Kita et al. [71] provided comprehensive experimental details, including internal standards, chromatographic parameters, and representative spectra. Such rigorous documentation is essential for reproducibility and offers valuable guidance for researchers aiming to establish robust workflows for oxylipin quantification.

8. Oxylipins in pain

Growing evidence indicates that an expanding array of lipid mediators, including oxylipins, contributes significantly to the development of nociceptive, inflammatory, and neuropathic pain. These bioactive lipids modulate pain by sensitizing sensory neurons, activating ion channels such as TRP receptors, and shaping neuroimmune interactions [73,74]. Understanding their roles in pain signaling provides critical insights into disease mechanisms and highlights potential targets for therapeutic intervention.

Oxylipins exert both pro- and anti-nociceptive effects through interactions with G protein-coupled receptors (GPCRs) and transient receptor potential (TRP) ion channels, including TRPV1 and TRPA1 [75]. AA derived metabolites, for example, play a central role in pain processing, with prostaglandins amplifying pain, and endocannabinoids (ECs) counteracting (Fig. 4) [73,76]. In addition to these well-characterized pathways, murine models of inflammatory and neuropathic pain have shown elevated levels of LA-derived oxylipins, including 9-HODE (twofold), 9,10-DiHOME (fourfold), and 12, 13-DiHOME (sixfold) [77] (Table 4). These changes, observed across paw, dorsal root ganglia, sciatic nerve, and spinal cord, have been linked to nociceptive sensitization via TRP channels activation [77–79].

Other LA-derived oxylipins, such as 9(10)- and 12(13)-EpOME, have been implicated in nociceptive signaling [82,86]. In a burn injury model, both EpOMEs and their diol metabolites (DiHOMEs) were elevated in spinal cord tissue, where they promoted mechanical and thermal allodynia via TRPV1 and TRPA1 activation [82]. These oxylipins were also detected in peripheral tissues of burn patients, with their circulating levels correlating with injury extension [82]. Similarly, in a model of chemotherapy-induced peripheral neuropathic pain, paclitaxel treatment increased 9(10)-EpOME synthesis, contributing to TRPV1-mediated hypersensitivity [86].

Dietary interventions further highlight the modifiability of oxylipin profiles and their relevance to pain modulation. Mice fed a LA-enriched diet exhibited elevated plasma levels of pro-nociceptive oxylipins, including 9-HODE, 13-HODE, 9-oxoODEs, 13-oxoODEs, 12,13-DiHOMEs, 9(10)-EpOMEs, and 12(13)-EpOMEs, which are capable of sensitizing TRPV1 nociceptors [80]. In contrast, an oleic acid-enriched diet increased levels of anti-nociceptive EPA and DHA-derived oxylipins, including 18-HEPE, 12-HEPE, and 4-HDoHE [80]. In humans, a clinical trial employing a diet high in omega-3 and low in omega-6 PUFA led to a reduction in headache severity and frequency, accompanied by increased plasma levels of 18-HEPE, 17-HDoHE, and resolvins [84]. While these findings underscore the influence of dietary lipids on pain modulation, further studies are needed to clarify the clinical significance of omega-3 and omega-6-derived oxylipins in human pain disorders.

In Achilles tendinopathy, increased serum levels of LA-derived oxylipins (HODEs, DiHOMEs, TriHOMEs) and AA-derived epoxyeicosatrienoic acids (EETs) have been detected, suggesting their involvement in non-inflammatory pain mechanisms. However, the authors noted technical limitations, particularly in sample preparation, reinforcing the need for methodological standardization [85].

Tissue injury triggers rapid local responses that coordinate both the initiation and resolution of inflammation and, consequently, pain. The inflammatory process involves increased levels of protein synthesis, modification and transport to support tissue repair and homeostasis [83]. In this context, mechanistic studies have uncovered pathways linking stress responses to prostaglandin biosynthesis in pain modulation. For example, IRE1α-XBP1 signaling regulates PG biosynthesis through COX-2 and mPGES-1 transcription. Mice lacking IRE1α exhibit reduced expression of these enzymes and lower levels of PGE_2, PGD_2, and $PGF_2\alpha$, alongside attenuated pain behavior [83]. Similarly, PGE_2-G, an oxidized metabolite of the endocannabinoid 2-AG via COX-2, is elevated in sensory neurons in a sickle cell disease model. Its inhibition attenuated hyperalgesia, underscoring its role as a novel pain mediator [81].

In summary, oxylipin profiling is revealing new key molecular pathways in pain modulation. By integrating dietary, transcriptomic, and lipidomic data, these studies reveal novel biomarkers and therapeutic targets, paving the way for more personalized and effective strategies to manage chronic pain. Interestingly, emerging evidence points to octadecanoid diols produced by CYP-sEH pathways (12,13-DiHOME, 9,10-DiHOME) as relevant pain modulators (Fig. 3D).

9. Oxylipin in skin diseases

The skin, the largest organ of the human body, plays vital structural, protective, and immunological roles. Environmental and intrinsic factors, including ageing, pollution, UV radiation, and microbiota composition, can disrupt the skin barrier functions influencing lipid

Table 3
Oxylipin species reported in selected publications on infectious diseases.

Disease	Population (illness/ control)	Sample	Up-regulated	Down-regulated	N° of Oxylipin Monitored	Conc. Range	Ref.
COVID-19	Human (45/25)	Bronchoalveolar Lavage (BAL)	PGE_2, TXB_2, 12-HHTrE, LTB_4		Not Specified	Not Specified	[63]
	Mice (10/5)	Bronchoalveolar Lavage (BAL)	12-HEPE, 12-HETE	PGD_2, $PGF_2\alpha$, TXB_2	Not Specified	Not Specified	[65]
	Human (33/25)	Bronchoalveolar Lavage (BAL)	PGE_2, TXB_2, PGD_2, $PGF_2\alpha$, 6-keto-$PGF_1\alpha$, 12-HHTrE, LTB_4, 20-hydroxy-LTB_4, 20-carboxy-LTB_4, 12-oxo-LTB_4, LTD4, LTE_4, 14,15-LTE_4, 5-HETE, 12-HETE, 15-HETE, 15-Oxo-ETE, 5,12-DiHETE, 5,15-DiHETE, LXA_4, 12-HEPE, 15-HEPE, 18-HEPE, 17-HDPA, 14-HDoHE, 17-HDoHE, PDX, RvD1, RvD2, RvD3, RvD4, RvD5, 9-HODE, 13-HODE, 13-oxo-ODE, 13-HOTrE, 15-HETrE		Not Specified	Not Specified	[59]
	Human (Severe: 20; Moderate: 18; Healthy: 19)	Blood Serum	*Moderate:* PGE_2, PGD_2, $PGF_2\alpha$, RvE3 *Severe:* HETE, DiHETEs		Not Specified	Not Specified	[61]
	Human (Severe: 8; Moderate: 8; Mild: 8; Healthy: 7)	Blood Serum	*All:* PGE_2 *Severe:* RvE1. RvD5, Mar2, 14-HDoHE		23	Not Specified	[66]
	Human (WT: 14; Alfa: 9; Delta: 11; Omicron: 14)	Blood Plasma	*WT:* overall oxylipin, specially SPMs *Omicron:* PGE_2, PGD_2, 20-F4t-NeuroP, 14-F_3t-NeuroP, 7(R,S)-ST-Δ^8-11-dihomo-IsoF *Delta:* increase in overall oxylipin compared to Alfa	*WT:* DiHETEs; Omicron: 8,9-DiHETE, ent-15-E2t-IsoP	60	0.1 pg/mL - 50 ng/mL	[62]
	Human (Critical: 23; Severe: 15)	Blood Plasma	*Severe:* LTB_4, LTD_4, LTE_4, LTC_4, RvD1, MCTR1, RvD3, NPD1	*Critical:* LTs, RvD1, RvD3	Not Specified	Not Specified	[60]
Bacterial and Viral Sepsis in COVID-19	Human (COVID: 164, non-COVID: 251; control: 16 - plasma)	Blood Plasma	*COVID/non-COVID vs CTR:* 15(RS)-F_2c-IsoP, 5-HETE, 15-HETE	*COVID vs non-COVID:* LTB_4, LTE_4, 12-HETE, 14,15-DiHETrE	18	Not Specified	[67]
	Human (COVID: 164, non-COVID: 251; control: 16 - plasma)	Urine	*COVID:* PGDM; *COVID/non-COVID vs CTR:* PGEM, PGDM, PGIM, 8,9-DiHETrE, 15-F_2t-IsoP, 9,10-DiHOME		18	Not Specified	[67]
Sepsis	Mice (11/13)	Serum and Peritoneal Lavage Fluid	PGE_2, LTB_4, 6-keto-$PGF_1\alpha$, 12-HETE		14	5–2000 pg injected	[68]
	Human (67/20)	Blood Plasma	$PGF_1\alpha$; 5(RS)-5-F2t-IsoP	5,6-DiHETrE, 9,10-DiHOME, 9(10)-EpOME/ 9,10-DiHOME and 12(13)-EpOME/12,13-DiHOME ratios	141	Not Specified	[64]
	Human (283/39)	Blood Plasma	12-HETE, 15-HETE, 11-HETE, 14-HDoHE		39	500 ng/mL - 100 pg/mL	[69]

(*continued on next page*)

Table 3 (*continued*)

Disease	Population (illness/ control)	Sample	Up-regulated	Down-regulated	N° of Oxylipin Monitored	Conc. Range	Ref.
	Mice (Not Specified)	Peritoneal Macrophages	*LPS:* PGE_2, PGD_2, $PGF_2\alpha$, 6-keto-$PGF_1\alpha$		106	0.3–2000 nM	[15]
Influenza (H1N1)	Human (44/44)	Blood Serum	11,12-DiHETrE, 14,15-DiHETrE, 8,9-DiHETrE, 17-HETE, 20-HETE, 12(13)-EpOME, 9(10)-EpOME	TXB_2, TXB_3, LTB_4	65	Not Specified	[70]
Bacterial Infection	Mice (Not Specified)	Murine Macrophage-like RAW264.7	*LPS:* PGE_2, PGD_2, $PGF_2\alpha$ *A23187:* LTC_4		14	5–2000 pg injected	[71]

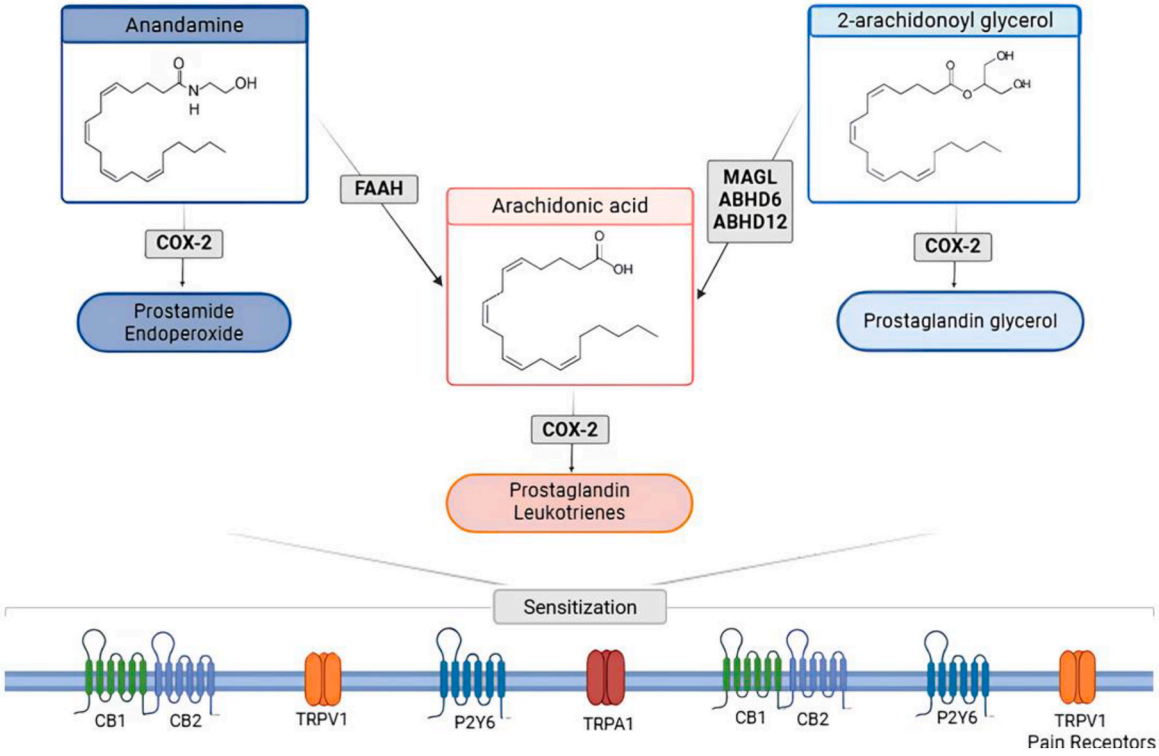

Fig. 4. Pain sensitization receptors and endocannabinoids. N-arachidonoyl-ethanolamine (anandamine) and 2-arachidonoyl glycerol (2-AG) are the two major endogenous cannabinoids. They can release free arachidonic acid through the action of specific enzymes, such as fatty acid amide hydrolase (FAAH), monoacylglycerol lipase (MAGL), α/β hydrolase domain 6 (ABHD6) and 12 (ABHD12). Both endocannabinoids can be oxygenated via COX-2. The product of the oxygenation of anandamide via COX-2 are prostamides and endoperoxides, while the oxygenation of 2-AG produces prostaglandin-glycerols. Both endocannabinoids and their products can sensitize pain pathway receptors such as cannabinoid receptor 1 (CB1) and 2 (CB2); TRP channels (TRPV1, TRPA1); and P2Y6 receptors.

metabolism and immune responses [87]. Importantly, skin lipids function not only as a physical barrier but also regulate inflammatory and immune process in diverse functions, such as cell signaling, inflammation, and immune responses [88–90].

9.1. Psoriasis (Ps) and psoriatic arthritis (PsA)

Psoriasis is an autoimmune disease that affects approximately 3 % of the global population and often results in pruritus or pain. A comparative analysis of mononuclear cells from patients with psoriasis vulgaris (Ps), psoriatic arthritis (PsA), and healthy controls revealed disruptions in lipid metabolism, including elevated levels of PGE_1, LTB_4, 13-HODE, and TXB_2. In contrast, 15-deoxy-$\Delta^{12,14}$-PGJ_2 and 15-HETE were increased in Ps but reduced in PsA [91] (Table 5). In another study, blood serum analysis revealed decreased levels of AA-derived proinflammatory oxylipins in both Ps and PsA, while increased amounts were observed in PsA patients associated with enthesitis, an inflammation of connective tissues between bones [92].

In psoriatic lesions, oxidative derivatives of LA, including 9-HODE, 13-HODE, 13-OH-9(10)-EpOME and 9,10,13-TriHOME, were markedly elevated [93,99]. Oxylipin quantification of both the free pool (free acids) and the total pool (esterified and free acids) revealed that total oxylipin concentrations were tenfold higher in the free pool, suggesting the skin's capacity to store oxylipins and release them as free acids for signaling. Furthermore, 13-OH-9(10)-EpOME and 9,10,13-TriHOME induced nociceptive behavior in mice, indicating a potential role in mediating acute pain responses in psoriasis [99].

9.2. Atopic dermatitis

Atopic dermatitis is a chronic epidermal dysfunction affecting 15–20 % global population, characterized by dry, ichthyotic, eczematous skin lesions, associated with Th2 immune response [89,90,96]. Both lesional and non-lesional atopic dermatitis skin showed upregulation of the

Table 4
Oxylipin species reported in selected publications on pain.

Disease	Population (illness/ control)	Sample	Up-regulated	Down-regulated	N° of Oxylipin Monitored	Conc. Range	Ref.
Pain	Rat (11/-)	Blood Plasma	*High linoleic acid diet:* 9-HODE, 13-HODE, 9-Oxo-ODE, 13-Oxo-ODE, 12,13-DiHOME, 12(13)-EpOME, 9(10)-EpOME, 5-HETE, 8-HETE, 5-oxo-ETE, 5(6)-EpETrE		52	0.11 ± 0.019–688.506 ± 283.089 ng/mL plasma	[80]
	Rat (12/-)	Blood Plasma	*High oleic acid diet:* 18-HEPE, 12-HEPE, 4-HDoHE, 19(20)-EpDPE, 7(8)-EpDPE, 14-HDoHE		52	0.054 ± 0.071–138.452 ± 59.590 ng/mL plasma	[80]
	Mice (Not Specified)	Paw	TXB_2, 13-HODE, 9-HODE, 12(13)-EpOME		11	Not Specified	[77]
	Mice (Not Specified)	Sciatic Nerve	13-HODE, 9,10-DiHOME, 12,13-DiHOME		11	Not Specified	[77]
	Mice (Not Specified)	Dorsal Root Ganglia (DRGs)	13-HODE, 9-HODE, 9,10-DiHOME		11	Not Specified	[77]
	Mice (Not Specified)	Spinal Cord		TXB_2	11	Not Specified	[77]
Nociception	Rat (4/-)	Hind Paw	PGE_2; *Carrageenan injection:* 9-HODE, 9,10-DiHOME, 12,13-DiHOMEs, TXB_2, 5-HETE		35	*Unsterified:* 0,01 - 0.79 ng/g; *Total:* 0.04–29.19 ng/g	[78]
	Rat (4/-)	Dorsal Horn of the Spinal Cord		*Carrageenan injection:* TXB_2	35	*Unsterified:* 0.01 - 0.79 ng/g; *Total:* 0.04–29.19 ng/g	[78]
Sickle Cell Disease	Mice (8/8)	Dorsal Root Ganglia (DRGs) - L2-L6 bilaterally	*HbSS:* PGE_2, PGE_2-G *HbSS + R-flutbipofren:* PGE_2	*HbSS + R- flutbipofren:* PGE_2-G	2	86 ± 17 fmol - 274 ± 35 pmol	[81]
Inflammatory pain	Mice (6/6)	Hind Paw	*CFA injection:* 12,13-DiHOME *Zymosan + TPPU:* 9(10)-EpOME; 12(13)-EpOME; 5(6)-EpETrE; 5,6-DiHETrE	*Zymosan injection:* 9(10)-EpOME, 12(13)-EpOME *Zymosan + TPPU:* 9,10-DiHOME, 12,13-DiHOME, 14(15)-EpETrE, 14,15-DiHETrE	14	*Zymosan:* 0.89-48.02 pg/mg; *CFA:* 2.33-22.61 pg/mg; *Zymosan + TPPU:* 0.15–46.54 pg/mg	[79]
	Mice (6/6)	Dorsal Horn of the Spinal Cord	*Zymosan injection:* 9,10-DiHOME, 12,13-DiHOME; *Zymosan + TPPU:* 5(6)-EpETrE; 5,6-DiHETrE, 14(15)-EpETrE	*Zymosan + TPPU:* 9,10-DiHOME, 12,13-DiHOME, 14,15-DiHETrE	14	*Zymosan:* 0.89-48.02 pg/mg; *CFA:* 2.33-22.61 pg/mg; *Zymosan + TPPU:* 0.15–46.54 pg/mg	[79]
Post-burn Mechanical and Thermal Allodynia	Rat (4–6/4–6)	Spinal Cord	9,10-DiHOME, 12,13-DiHOME, 9(10)-EpOME 12(13)-EpOME		8	2–8 ng/g tissue	[82]
IRE1a-deficiency	Bone Marrow–Derived Dendritic Cells (BMDCs) (3/4)	Cell Lysates		*LPS:* PGE_1, $PGF_1\alpha$, PGD_2, PGE_2, $PGF_2\alpha$, 15-keto-$PGF_2\alpha$, Δ^{12}-PGJ_2, 13,14-dehydro-15-keto-PGE_2, PGD_3	6	Not Specified	[83]
	Leukocyte IRE1a KO Transgenic Mice (Not Specified)	Cell Free Peritonial Lavage		*Zymosan:* PGE_2, PGD_2, $PGF_2\alpha$, TXB_2	6	Not Specified	[83]
Chronic Headaches	Human (H3-L6 diet: 33, L6 diet: 34)	Blood Plasma	18-HEPE, 17-HDoHE, RvD2	9-HODE, 13-HODE, 9-oxo-ODE, 13-oxo-ODE, 5-HETE, 8-HETE, 9-	13	*n-3 derived:* 30.7–289.9 pg/mL; *n-6 derived:* 31.8–72.3 nM	[84]

(*continued on next page*)

Table 4 (*continued*)

Disease	Population (illness/ control)	Sample	Up-regulated	Down-regulated	N° of Oxylipin Monitored	Conc. Range	Ref.
				HETE, 11-HETE, 12-HETE, 15-HETE			
Achilles Tendinopathy	Human (15/16)	Blood Plasma	9-HODE, 13-HODE, 9,10-DiHOME, 12,13-DiHOME, 9,10,13-TriHOME, 9,12,13-TriHOME, 5(6)-EpETrE, 11(12)-EpETrE		37	0–152000 pg/mL	[85]

12/15-LOX and COX pathways, alongside reduced n-3/n-6 PUFA ratios and their metabolites, indicative of a pro-inflammatory and non-resolving lipid mediator profile [96]. Targeted LC-MS/MS analyses of urinary oxylipins in both DNFB-induced atopic dermatitis-like mouse models and children with atopic dermatitis revealed elevated levels of COX-derived prostaglandin metabolites, particularly those derived from PGD_2, PGE_2, and $PGF_2\alpha$. These increases were specific to atopic dermatitis and not observed in non-allergic dermatitis models, consistent with upregulated mRNA and protein expression of $PGF_2\alpha$, PGE_2, and PGD_2 synthase in DNFB-treated skin. Additional increases in PGI_2 metabolites and 17-HETE were also detected in atopic dermatitis patients. These findings highlight urinary oxylipins as potential non-invasive biomarkers and provide novel insights into the pathophysiology of atopic dermatitis [97].

9.3. *Hidradenitis suppurativa (HS)*

Hidradenitis suppurativa (HS) is characterized by painful nodules, abscesses, and fistulas caused by chronic inflammation of the hair follicles and sebaceous glands [89,90,98]. Comparative plasma lipidomic profiling revealed elevated levels of LOX- and CYP-sEH-derived oxylipins, including 15-HETE, 11,12-DiHETrE and 14,15-DiHETrE, which were associated with HS severity [98]. In a broader study using plasma samples from Ps, atopic dermatitis and HS patients, the CYP-sEH-derived oxylipins 16,17-DiHDPE, 19,20-DiHDPE and DiHETrEs were identified as specific to atopic dermatitis and HS. Their depletion was linked to impaired PPAR activation and reduced reactive oxygen species scavenging capacity in these patients [89,90].

9.4. *Conclusions*

In conclusion, altered oxylipin profiles are closely associated with various skin disorders and disruptions in skin homeostasis, often stemming from barrier dysfunction. This imbalance is largely linked to enzymatic and non-enzymatic oxidation of skin lipids. While eicosanoids have historically been the most extensively studied oxylipins in skin, growing attention in now directed toward octadecanoids. Dysregulation of these oxylipin metabolites highlights their potential as biomarkers for specific dermatological conditions. Elevated levels of pro-inflammatory oxylipins, such as n-6 derived prostaglandins (e.g., PGE_2, $PGF_2\alpha$) and lipoxygenase metabolites (e.g., LTB_4, 12-HETE, 13-HODE) are frequently detected (Fig. 3E) and correlate with disease severity in inflammatory skin disorders, such as atopic dermatitis and psoriasis. It is also worth noting that, beyond localized effects in the skin, oxylipin imbalances may contribute to systemic manifestations, such as pain, further highlighting the interconnected nature of skin-derived lipid mediators in broader physiological responses. Although advances in analytical techniques, including minimally invasive sampling strategies, are facilitating oxylipin detection, elucidating the precise mechanistic links between specific lipid mediators and disease pathophysiology remains a critical focus for future research.

10. Future directions in oxylipin biology and therapeutics

Over the past decades, advances in analytical techniques for oxylipin profiling have enabled the identification and quantification of numerous oxylipins that function as signaling molecules and bioactive inflammatory lipid mediators. These oxidized lipids contribute to the pathophysiological mechanisms underlying multiple human diseases. Oxylipins exert their biological effects through the activation or inhibition of distinct cellular receptors, while their *in vivo* availability depends on enzymes involved in their biosynthesis and degradation. These insights opens opportunities to target both oxylipin receptors and enzymes regulating their metabolism as therapeutic strategies in diseases involving oxidized lipids.

In various diseases, including neurodegenerative, metabolic, and infectious diseases, as well as pain-related and skin disorders, the overexpression or downregulation of oxylipin-generating enzymes such as cyclooxygenases (COXs), lipoxygenases (LOXs), cytochrome P450s (CYPs), and soluble epoxide hydrolase (sEH) has been directly associated with altered oxylipin profiles in tissues and biological fluids. Small molecules acting as inhibitors or activators of COXs, LOXs, CYPs and sEH, have been discovered and developed over decades, as reviewed in the literature [100–103], with some already in clinical use, such as non-steroidal anti-inflammatory drugs (NSAIDs) targeting COXs, and zileuton, a 5-LOX inhibitor which is used to treat asthma. Nevertheless, as highlighted throughout this review, much remains to be clarified and explored regarding the therapeutic potential of LOXs, COXs, CYPs, sEH, and other enzymes in regulating oxylipin levels across human diseases. Therefore, discovering selective, isoform-specific, structurally diverse, and drug-like inhibitors targeting these enzymes remains crucial for elucidating their specific biological roles and, ultimately, for drug development. The same applies to membrane receptors that mediate the biological actions of oxylipins. Table 6 provides an overview of the major enzyme families and receptors associated with oxylipin biosynthesis and signaling that have been reported as altered in the diseases discussed here, highlighting their potential as therapeutic targets.

The enzyme families catalyzing oxylipin formation exhibit structural specificities in terms of: (i) overall fold, tertiary and quaternary structures, and structural flexibility; (ii) physicochemical and spatial properties of their binding sites, which define substrate affinities; (iii) and the presence of ion(s) and/or prosthetic groups as cofactors. Although these features must be considered on a case by case in inhibitor design, enzymes producing oxylipins, such as LOXs, typically possess hydrophobic substrate-binding sites capable of accommodating lipid substrates or other hydrophobic ligands, including lipophilic inhibitors [104]. While lipophilic groups buried within hydrophobic protein pockets can enhance inhibitor-enzyme binding affinity, high lipophilicity often results in low aqueous solubility, poor bioavailability, and unfavorable pharmacokinetic properties [105]. In cases where central nervous system activity is required, the ability of inhibitors to cross the blood-brain barrier must also be addressed. Thus, an appropriate balance of lipophilicity, water solubility, size, and polarity is critical in the

Table 5
Oxylipin species reported in selected publications on skin diseases.

Disease	Population (illness/control)	Sample	Up-regulated	Down-regulated	N° of Oxylipin Monitored	Conc. Range	Ref.
Psoriasis (PS)	Human (Ps: 32; PsA: 16, healthy: 16)	Lymphocytes Eriched Fraction from Blood	*Psoriasis vulgaris (Ps) and arthitis (PsA):* PGE_1, LTB_4, 13-HODE, TXB_2; *Ps:* 15-deoxy-$\Delta^{12,14}$-PGJ_2, 15-HETE; *PsA:* 15-F_2t-IsoP, 4-HNE	*PsA:* 15-deoxy-$\Delta^{12,14}$-PGJ_2, 15-HETE	6	Up to 450 pmol/mg of protein	[91]
	Human (PsO: 20, PsA: 19)	Blood Serum	*PsA:* 5,15-DiHETE, 5-oxo-ETE, PGE_2, 11β-PGE_2, LTB_4	*PsA patients with higher skin scores:* PGE_2, $PGF_2\alpha$, 8,15-DiHETE, 15-oxo-ETE; *PsO patients with higher skin scores:* PGD_1, PGD_3, 11-HEPE, 4-HDoHE.	66	Not Specified	[92]
	Human (9/5)	Tape strip	9- or 13-HODE; 9,10,13- or 9,12,13-triHOMEs		Not Specified	14.4–19.7 ng/mg	[93]
	Human (3/3)	Fibroblasts and Keratinocytes (Psoriac Substitutes)	PGE_2, 9-HODE, 15-HETE; *ALA supplementation:* PGE_3, 13-HOTrE, 15-HEPE, 18-HEPE	*ALA supplementation*: PGE_2, 15-HETE, 9-HODE	18	0.5–50412.4 pmol/g of tissue	[94]
	Rat (12/12)	Dermal interstitial fluid (dISF)	12-HETE, 15-HETE, LTB_4, TXB_2, $PGF_2\alpha$, PGE_2, PGD_2, 17-HDoHE, 12-HEPE, 5-HETE		11	Not Specified	[95]
Atopic Dermatitis (AD)	Human (6/6)	Skin (affected and non-afected)	5-HETE, 11-HETE, LTB_4, PGJ_2, 4-HDoHE, 10-HDoHE;		Not Specified	0.1–370.0 ng/g of tissue	[96]
	Human (6/6)	Blood Serum	13-HODE	LXA_4, LTB_5, Mar	Not Specified	0.1–100.0 ng/mL	[96]
	Human (10–14/3–4)	Urine	PGD_2, PGE_2, PGI_2, $PGF_2\alpha$, 15-keto-$PGF_2\alpha$, 13,14-dihydro-15-keto-tetranor-$PGF_1\alpha$, 20-hidroxy-PGE_2, 15-keto-PGE_2, 13,14-dihydro-15-keto-tetranor-PGE_2, 13,14-dihydro-15-keto-PGJ_2, 6-keto-$PGF_1\alpha$, 6,15-diketo-13,14-dihydro-$PGF_1\alpha$		138	Not Specified	[97]
	Mice (6–8/-)	Urine	PGD_2, PGE_2, $PGF_2\alpha$, PGK_2, 15-keto-PGE_2, 14,15-dihydro-15-keto-PGE_2, 14,15-dihydro-15-keto-tetranor-PGE_2, 6-keto-$PGF_1\alpha$, 13,14-dihydro-15-keto-tetranor-$PGF_1\alpha$, 13,14-dihydro-15-keto-tetranor-$PGF_1\beta$, 13,14-dihydro-15-keto-PGJ_2, 11β-13,14-dihydro-15-keto-$PGF_2\alpha$		138	Not Specified	[97]
Hidradenitis Suppurativa (HS)	Human (60/73)	Blood Plasma	*HS:* 15-HETE, 11,12-DiHETrE, 14,15-DiHETrE; *Severe:* 11-HETE, 11,12-DiHETrE, 14,15-DiHETrE	*Severe:* 9,10-DiHOME	16	Not Specified	[98]
Psoriasis (PS), Atopic Dermatitis (AD) and Hidradenitis Suppurativa (HS)	Human (PS: 15; AD: 15, HS: 15, Healthy: 12)	Blood Plasma	*AD:* 9-HODE, 13-HODE	*HS:* 16,17-DiHDPE, 19,20-DiHDPE; *AD/HS:* DiHETrEs	Not Specified	Not Specified	[89, 90]

development of drug-like inhibitors of oxylipin-producing enzymes. These physicochemical properties directly affect inhibitory potency, cell membrane permeability, and pharmacodynamic and pharmacokinetic properties. Ideally, they should be considered early in drug design process, or optimized during hit-to-lead development.

In addition to its role in oxylipin biosynthesis, lipid peroxidation plays a pivotal role in cell death. Extensive (phospho)lipid peroxidation has been recognized as the primary driver of ferroptosis, an iron-

Table 6
Enzymes (and/or enzyme families) and cell receptors that play a role in the biosynthesis and/or mode of action of oxylipins whose levels were found altered in the neurodegenerative, metabolic, infectious, pain-related, and skin diseases covered in this review.

Group of Diseases	Disease	Enzymes (and/or enzyme families) and/or cell receptors with a role in oxylipins' biosynthesis or mode of action	Ref.
Neurodegenerative Diseases	Alzheimer's Disease	CYPs and sEH	[23] [27] [24] [38]
		COXs	[26]
		LOXs (such as 15-LOXs and 5-LOX)	[26]
	Parkinson's Disease	CYPs and sEH	[40]
		COXs	[36]
		LOXs (such as 15-LOXs)	[36]
	Multiple Sclerosis	CYPs and sEH	[34]
		COXs	[32] [42] [35]
		LOXs (such as 15-LOXs and 5-LOX)	[32] [33]
	Amyotrophic Lateral Sclerosis	CYPs and sEH	[28] [29]
		COXs	[29]
		LOXs (such as 5-LOX)	[29] [45]
Metabolic Diseases	Obesity	CYPs and sEH	[50] [56]
		COXs	[49]
		LOXs	[48] [51] [49]
Infectious Diseases	COVID-19	COXs	[59] [62] [63]
	Sepsis-associated kidney injury	CYPs and sEH	[64]
Pain-Related Diseases	Nociceptive, inflammatory, and neuropathic pain	CYPs and sEH	[77]
		COXs (such as COX-2)	[83] [81]
		Pain pathway receptors, CB1 and CB2; TRPV1 and TRPA1; and P2Y6	[75] [78] [77] [79] [82] [80]
		IRE1α and XBP1	[83]
Skin Diseases	Psoriasis and Psoriatic Arthritis	CYPs and sEH	[93] [99]
		COXs	[91]
		LOXs	[91]
	Atopic Dermatitis	COXs	[96]
		LOXs (such as 15-LOX-1)	[96]
	Hidradenitis Suppurativa	CYPs and sEH	[98] [89, 90]
		LOXs	[98]
		PPAR	[89, 90]

dependent oxidative form of cell death that has attracted scientific attention in recent years [106]. The underlying mechanisms involve the physical disruption of cellular membranes, leading to loss of integrity, and the formation of electrophilic species that covalently modify proteins and other essential biomolecules. Additionally, phospholipid hydroperoxides and their downstream products (e.g., hydroxides, epoxides, and aldehydes) can further amplify immune responses [107–109].

The interplay between ferroptosis and oxylipin production responses has yet to be fully elucidated. Nevertheless, pharmacological modulation of lipid peroxidation has attracted considerable interest. On one hand, small-molecule antioxidants that inhibit enzymatic and non-enzymatic lipid peroxidation, thereby preventing ferroptosis, hold therapeutic potential for diseases in which lipid peroxidation plays a role in pathology. On the other hand, targeted induction of ferroptosis by promoting lipid peroxidation has emerged as a promising strategy for treating tumors, particularly those resistant to standard therapies.

CRediT authorship contribution statement

Larissa R. Diniz: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Rosangela S. Santos:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Hector Oreliana:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Ana Clara A. Zucão:** Writing – review & editing, Writing – original draft, Formal analysis. **Megumi N. Yukuyama:** Writing – review & editing, Writing – original draft, Formal analysis. **Guilherme R.S. Resende:** Writing – review & editing, Resources. **Thais Satie Iijima:** Writing – review & editing, Writing – original draft. **Lucas G. Viviani:** Writing – review & editing, Writing – original draft. **Sayuri Miyamoto:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary data

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