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Moving forward with isoprostanes, neuroprostanes and phytoprostanes: where are we now?

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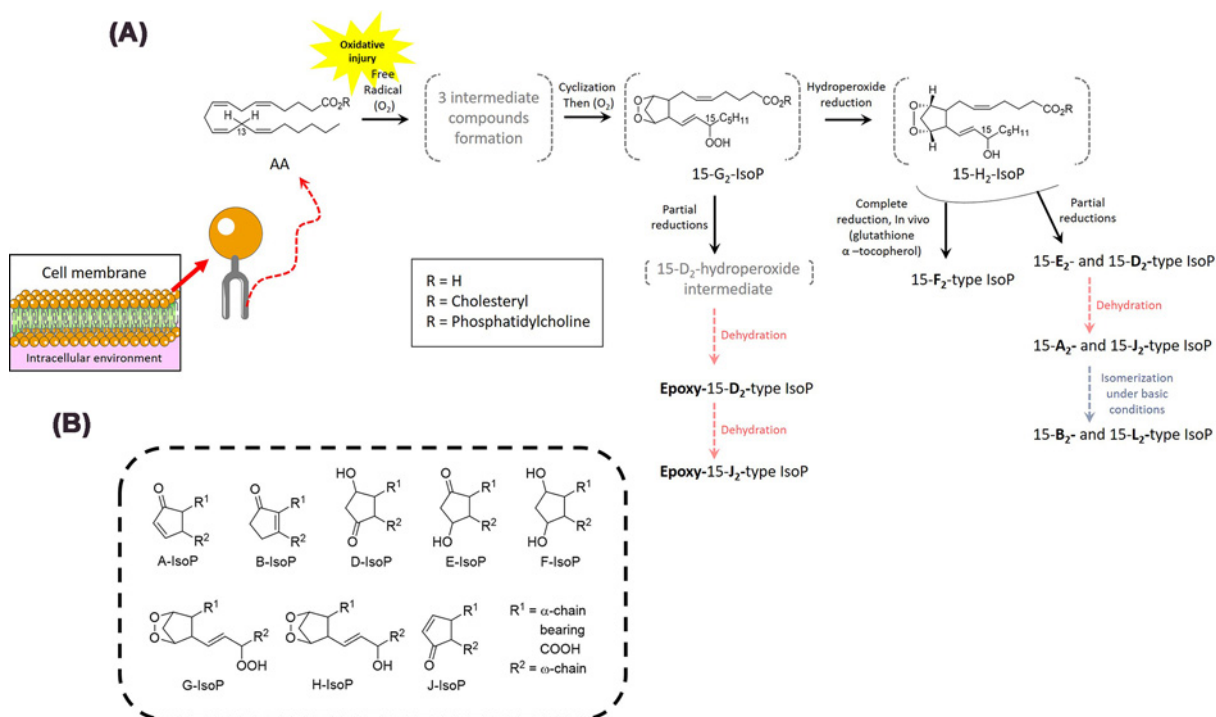
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Polyunsaturated fatty acids (PUFAs) are essential components in eukaryotic cell membrane. They take part in the regulation of cell signalling pathways and act as precursors in inflammatory metabolism. Beside these, PUFAs auto-oxidize through free radical initiated mechanism and release key products that have various physiological functions. These products surfaced in the early nineties and were classified as prostaglandin isomers or isoprostanes, neuroprostanes and phytoprostanes. Although these molecules are considered robust biomarkers of oxidative damage in diseases, they also contain biological activities in humans. Conceptual progress in the last 3 years has added more understanding about the importance of these molecules in different fields. In this chapter, a brief overview of the past 30 years and the recent scope of these molecules, including their biological activities, biosynthetic pathways and analytical approaches are discussed.

Introduction

The discovery of isoprostanes (IsoPs) in the nineties was a breakthrough in free radical biology [1]. These prostaglandin like molecules are generated through oxidation of polyunsaturated fatty acids (PUFA) via free radical, without the participation of cyclooxygenase (COX) enzyme [2]. The most well investigated IsoPs are those generated from arachidonic acid (AA) which is frequently used as oxidative stress biomarkers in biological systems. IsoPs are also known to mediate numerous diseases and to have a significant role in different pathologies, such as hypertension and ischaemic events [3] while physiologically it is found to be a vasoconstrictor [4].

Biologically, IsoPs exert their effect through intracellular signaling via kinase receptors (tyrosine and *Rho*) [5] and activation of prostanoid receptors [6]. IsoPs can be described as geometric isomers of prostaglandins (PGs) where the lateral chains of IsoPs are in *cis* configuration compared with the *trans* configuration of PGs. Unlike PGs, as noted, the biosynthesis of IsoPs do not require COX activation and instead, are catalysed by reactive oxygen species (ROS) through free radical reactions [7]. While PGs are generated from free AA, IsoPs are predominantly formed *in situ* from oxidation of AA esterified to phospholipids (i.e. glycerophospholipids, mainly phosphatidylcholine) in the membrane. Further studies unveiled that AA bound to phospholipids was oxidized *in vivo* to generate racemic IsoPs. In fact, approximately equal amount of all possible stereoisomers of the two lateral chains on the cyclopentane can be formed via this auto-oxidative process, therefore one-fourth of these isomers possess the 1,2-stereostructure of PGs and are independent of the COXs activity (see section 'IsoPs as oxidative stress biomarkers' for further discussion). They are released from the phospholipid backbone as free acids by phospholipase A₂ enzyme as well as platelet activating factor acetyl hydrolases [8]. Several classes of IsoPs can be formed, but the F₂-IsoPs, especially 15-F_{2t}-IsoP is the prominent and well-investigated biomarker to date, for assessing oxidative stress *in vivo* [8]. The free 15-F_{2t}-IsoP can be further metabolized through



Scheme 1. Chemical biosynthesis of isoprostanoids

(A) Chemical biosynthesis of IsoPs type A, D, E, F and J and epoxy-isomers (only the 15-IsoP series is displayed) [14]. **(B)** IsoPs classification according to their ring substitution pattern; IsoP, Isoprostanone.

β -oxidation and reduction to release 2,3-dinor-15-F_{2t}-IsoP and 2,3-dinor-5,6-dihydro-15-F_{2t}-IsoP respectively, and then excreted in urine [9].

Isoprostanoids such as neuroprostanes (NeuroPs) and phytoprostanes (PhytoPs) are oxidized products of docosa-hexaenoic acid (DHA) and α -linolenic acid (ALA), respectively. Aside from their importance as lipid biomarkers of oxidative stress in plants (PhytoPs) and mammals (NeuroPs), the emergence of the biological activities has attracted attention in recent years [10–13]. Although their formation follows the same pattern as the IsoPs pathways, their metabolism and excretion are not well illustrated.

In this chapter, a brief overview of past 30 years on the study of isoprostanoids, i.e. IsoPs, NeuroPs and PhytoPs and recent findings are discussed [14].

***In vivo* formation of isoprostanoids (biosynthesis)**

IsoPs are geometric isomers of PGs where the lateral chains of IsoPs are in *cis* configuration compared with the *trans* configuration of PGs. The biosynthesis of PGs and the role of COX enzymes have been investigated since late 50s [15,16]. Three decades ago, IsoPs were unveiled by Morrow and co-workers by exposing carbon tetrachloride to rats and nonsteroidal anti-inflammatory drugs to humans [7]. Explicit biosynthesis of IsoPs has been reported previously by our group [14], and will not be elaborated in this chapter. Briefly, as shown in (Scheme 1A), AA is a PUFA containing three *bis*-allylic moieties that are found in the phospholipid bilayer of the cell membrane. ROS initiates free radical chain reaction on AA under oxidative stress and in the absence of a sufficient repair mechanism, it leads to cell membrane damage.

Numerous intermediates are generated in the biosynthesis which eventually lead to the formation of G₂-IsoP type intermediate. The hydroperoxide of G₂-IsoP is further reduced to form the H₂-IsoP type intermediate. Several IsoP families could be formed from the H₂-IsoP depending on the degree of reduction. Their classifications according to their ring substitution pattern are shown in Scheme 1B. Complete reduction of endoperoxide leads to the formation of F₂-type of IsoPs (cyclopentane ring with two alcohol functions) while partial reduction leads to the formation of D₂- and E₂-types of IsoPs where the cyclopentane bears a hydroxy-ketone group. The ketone moiety on the cyclopentane of the E₂-IsoP type is in the neighbouring position in the α -chain (chain bearing the carboxyl group) whereas the hydroxyl is situated next to the second ω -chain and vice versa in the case of D₂- type IsoP. The ratio between F₂-

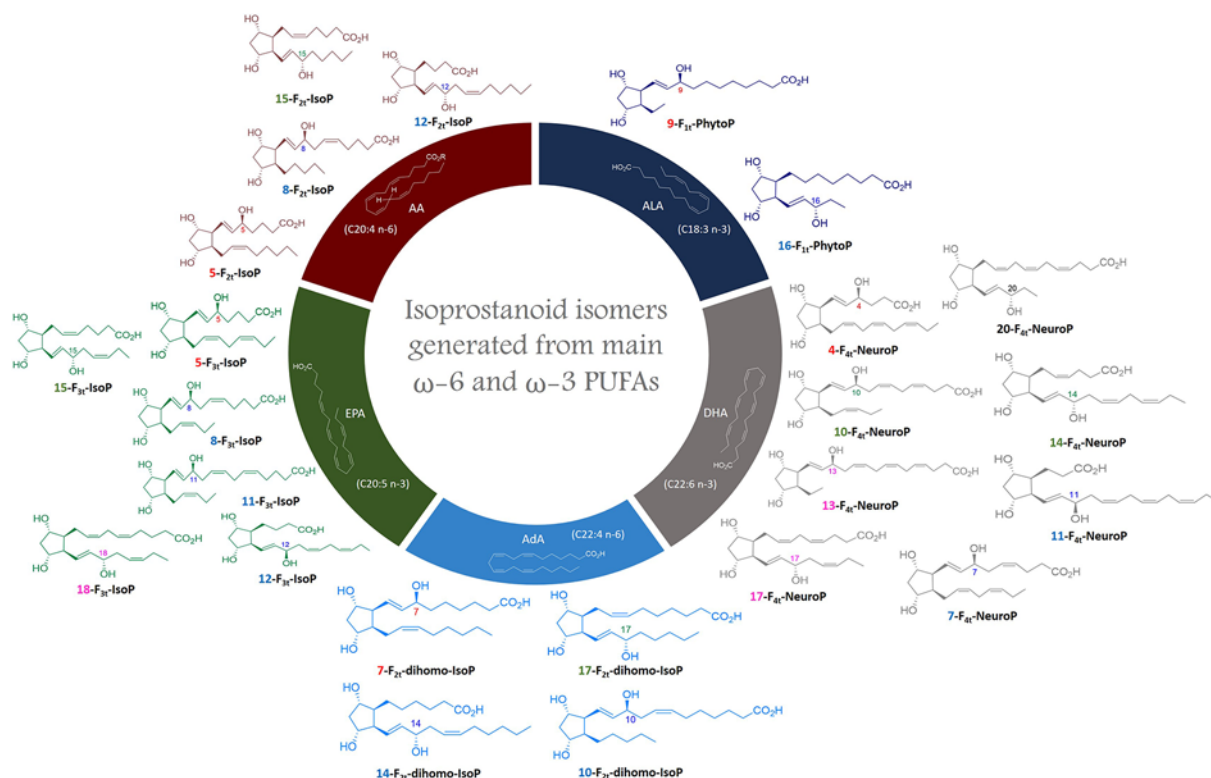


Figure 1. Isoprostanoids derived from ω -6 and ω -3 polyunsaturated fatty acids (PUFAs)

AA, arachidonic acid; AdA, adrenic acid; ALA, α -linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

D₂- and E₂- type IsoPs mainly depends on the number of reducing agents, e.g. glutathione and α -tocopherol, in cells [17]. Furthermore, dehydration can occur under physiological conditions, especially for types D₂- and E₂-IsoPs due to the presence of hydroxy-ketone structures. Subsequently, dehydration of E₂- and D₂- type IsoPs (red arrows) leads to the formation of A₂- and J₂-type IsoPs, respectively.

Other IsoP metabolites such as the epoxy-IsoPs are also formed after dehydration of the hydroperoxy-D₂-IsoP intermediate and from G₂-type IsoP after partial reduction. Dehydration occurs due to the acidity of the α -keto hydrogen atom and the activity of hydroperoxy forming epoxy-D₂. IsoP, which then again dehydrates spontaneously to epoxy-J₂-IsoP. These epoxy-IsoPs were identified in mildly oxidized LDL and in atherosclerotic lesions [18,19], and more recently, they are suggested to be potent anti-inflammatory lipid mediators [20]. Under basic conditions, the isomerization of the double bonds in A₂- and J₂- type IsoPs leads to the formation of B- and L-type IsoPs where they are thermodynamically more stable metabolites (blue arrows as shown in Scheme 1A).

Different series of IsoP can be formed from AA based on the site of free radical attack and oxygen trapping position. Hydrogen abstraction on C7 of AA will give the 5-IsoP series, whereas 8- and 12-IsoPs are produced through C10 hydrogen abstraction. In summary, four series of IsoPs starting from AA could be formed: 5-, 8-, 12- and 15-IsoPs where the 5- and the 15-series are the most abundant [14,21,22]. Considering the unique formation of F-type IsoPs, each series give rise to 16 different IsoP isomers (enantiomers included) hence, a total of 64 stereoisomers are potentially formed *in vivo* [14]. Figure 1 represents isoprostanoids generated from AA (in dark red part of the circle) and similarly from other ω -6 and ω -3 PUFAs.

ω -6 PUFA, adrenic acid (AdA, C22:4 n-6, blue part of the circle in Figure 1) is largely found in the adrenal gland and white matter of the brain. It has a similar structure as AA, but has two additional saturated carbons on the carboxyl end. Non-enzymatic oxidized products derived from AdA, namely dihom-IsoPs were introduced by Van-Rollins and co-workers [23]. Four series of dihom-IsoPs are produced by AdA oxidation, including 7-, 10-, 14- and 17-dihomo-IsoPs (blue part of the circle in Figure 1) where the 7- and 17-dihomo-IsoPs are the most abundant.

Of the ω -3 PUFAs, α -linolenic acid (ALA, C18:3 n-3, dark blue part of the circle in Figure 1) is predominantly found in plant leaves. Isoprostanoids of ALA were discovered by Mueller and co-workers in late nineties and were named phytoprostanes (PhytoPs) [24]. As shown in Figure 1 (dark blue part of the circle), ALA contains two *bis*-allylic

positions (C11 and C14) leading to two series of F-type PhytoPs; the 9-series and the 16-series, giving rise to 32 isomers (enantiomers included).

Intake of ω -3 PUFAs rich fish oil appeared to improve cardiac outcomes and exert cardioprotective effect as well as lower blood pressure [25,26]. It is hypothesized that the release of metabolites via non-enzymatic oxidation of eicosapentaenoic acid (EPA) and DHA [27] are responsible for the bioactive effects. Fish contains large amounts of ω -3 PUFAs, EPA (20:5 n-3, green part of the circle, Figure 1) and DHA (22:6 n-3, grey part of the circle, Figure 1). Indeed, EPA and DHA are concentrated in vertebrate brain, and it is acknowledged that intake of EPA and DHA are effective in improving depression, cognitive functions and modulate oxidative injury in Rett syndrome (RTT) [28]. The four *bis*-allylic positions at EPA will generate six series of IsoPs (5-, 8-, 11-, 12-, 15- and 18-IsoP, green part of the circle, Figure 1) where the 5- and 18-IsoPs series are the most abundant [29]. DHA is highly enriched in the grey matter of the human brain, cerebral cortex, skin and retina [30,31]. When peroxidised, eight series of NeuroPs can be formed (4-, 7-, 10-, 11-, 13-, 14-, 17- and 20-NeuroPs, grey part of the circle, Figure 1), where the 4- and 20-series are the most abundant [32].

Although isoprostanooids are predominantly generated in *in vivo*, a unique group of molecules can arise preferentially under increased cellular oxygen tension. In the biosynthesis, 2,3,5-trisubstituted tetrahydrofuran structures known as isofurans (IsoFs) are formed from AA [33], dihomofurans (dihomo-IsoFs) from AdA [34] and neurofurans (NeuroFs) from DHA [35]. More recently, it was discovered that ALA can also form isofuranoids and are named as phytofurans (PhytoFs) [36].

Metabolism

Metabolism of IsoPs has been well described for 15-F_{2t}-IsoP [37]. When released from the phospholipid via PLA₂ enzyme, the free 15-F_{2t}-IsoP is β -oxidized to form an intermediate compound, 2,3-dinor-15-F_{2t}-IsoP. This molecule then undergoes reduction to form 2,3-dinor-5,6-dihydro-15-F_{2t}-IsoP for urinary excretion [9]. Another alternative pathway of β -oxidation was discovered in rodents where 2,3-dinor-15-F_{2t}-IsoP can be reduced to 2,3,4,5-tetranor-15-F_{2t}-IsoP [38,39]. The metabolic pathway of 15-F_{2t}-IsoP is depicted in Scheme 2.

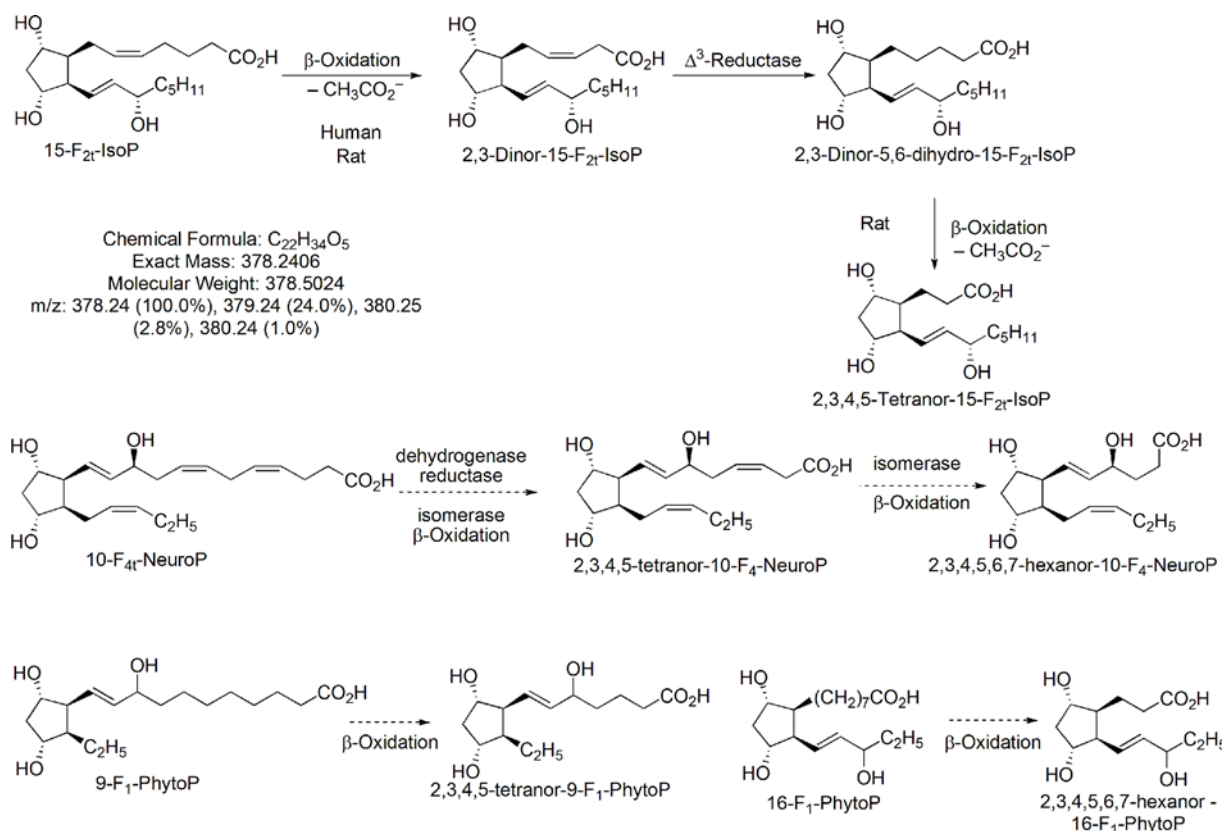
Studies on the metabolism of NeuroPs and PhytoPs are rather limited. Recently, our group showed infusion of 4-F_{4t}-NeuroP in the lateral tail vein of rodents displayed a fast uptake (30 s) in the liver and plasma while it took approximately 2 h in the brain. Importantly, 4-F_{4t}-NeuroP was able to pass the blood-brain barrier and mediate anti-inflammatory molecules derived from enzymatic oxidation of DHA [40]. Further, 4-F_{4t}-NeuroP stimulated antioxidant hemoxygenase-1 gene in neuronal cells and potentially posed to have a regulatory role for cell survival [40]. Some human and animal studies found NeuroPs, specifically 4-F_{4t}-NeuroP and 10-F_{4t}-NeuroP, were related to neurological disorders [32,41]. Interestingly, 4-F_{4t}-NeuroP was obviously abundant in circulation, but much less in urine, whereas 10-F_{4t}-NeuroP was clearly detectable in both body fluids in these neurological disease patients [42]. Uniquely, one isomer of NeuroP, the 7-F_{4t}-NeuroP, was shown to β -oxidized into another EPA-derived isoprostanooid, the 5-F_{3t}-IsoP in human urine [29].

There is a large room to explore in the metabolism of PhytoPs. However, reports are scarce and so far, only two are available in regards to human metabolism. Karg and co-workers found in healthy males who ingested plant oil had slow PhytoPs absorption and excretion [12]. Similarly, Barden et al. revealed that ingestion of ALA (flaxseed oil) increased F₁-PhytoP production in healthy human plasma but not in urine [43].

Like 15-F_{2t}-IsoP, it is anticipated that the metabolic clearance of NeuroPs and PhytoPs would be similar. As shown in Scheme 2 (dotted lines), it is hypothesized that through β -oxidation and reduction process, 10-F_{4t}-NeuroP would lead to the generation of 2,3,4,5-tetranor-10-F_{4t}-NeuroP and 2,3,4,5,6,7-hexanor-10-F_{4t}-NeuroP, and 9-F₁-PhytoP to 2,3,4,5,6,7-hexanor-16-F₁-PhytoP. These are stable end-products in the metabolism, therefore, pose to be attractive candidates for oxidative damage biomarker in urine, in particular, those of 10-F_{4t}-NeuroP for non-invasive assessment of oxidative injuries related to neurological functions.

Isoprostanooid analysis

Generation of ROS is a hallmark of oxidative injury [3]. Insofar, determining plasma or urinary 15-F_{2t}-IsoP is the most reliable biomarker for assessing oxidative damage in human. Method of IsoPs measurement in plasma was first developed by Morrow et al. using gas chromatography-mass spectrometry (GC-MS) [44]. Interestingly, the group noticed that during storage of plasma at -20°C for several months markedly increased the levels of PG-like compounds by approximately 50 times compared with the levels detected in fresh plasma. After structural elucidation of these compounds, Morrow named the prostaglandin-like compounds as isoprostanes [3].



Scheme 2. Metabolic Pathway of isoprostanoids

End-products of 15-F_{2t}-IsoP found in the metabolic pathway and hypothetical end-products of 10-F_{4t}-NeuroP and 9-F_{1t}-PhytoP.

Since then, a large number of eicosanoid metabolites originating from non-enzymatic free radical peroxidation of different PUFAs including AA, AdA, ALA, EPA, docosapentaenoic (DPA) and DHA were identified. [8,45] The analysis of these metabolites is challenging for several reasons. The first reason is the difficulty to distinguish between the enzymatic and non-enzymatic products, and the isomeric compounds, including those of geometrical and positional isomers [46]. Another reason is the very low concentration of isoprostanoids in biological samples require off-line sample concentration techniques or expensive analytical tools for sensitive detection. Lastly, artefacts of isoprostanoids can develop during sample preparation and may create biased analysis in biological specimens [43]. Several sample preparation and analytical techniques were published over the recent few years and discussed below.

Sample handling

As indicated, sample handling is a crucial step prior to isoprostanoids analysis to avoid *ex vivo* artefact formation. A detailed report has been made by Barden and co-workers on procedures for sample handling [43]. Only a few highlights are noted here. Before storage, oxygen should be eliminated from the samples by flushing with nitrogen or argon [47,48]. Light should be avoided by storing the samples in amber glass bottles or vials, aluminium foil protected vials without headspace or dark polystyrene pots with screw caps for larger volumes until analysis. A suitable antioxidant such as butylated hydroxytoluene (BHT), triphenylphosphine (TPP), diethylene tri-amine pentaacetic acid (DTPA) or glutathione (GSH) should be added [48–52]. A small amount of a COX inhibitor, e.g. indomethacin, can also be added to avoid *ex vivo* production [53,54]. In addition, biological fluids (i.e. blood, plasma, urine and sperm), tissues [55] and plant extracts [56] must be stored at ultra-low temperature (i.e. -80°C) without freeze-thaw cycles, to ensure stable shelf-life (6 months for plasma and 1–2 years for urine). Finally, for extracted sample in small volume, it is recommended to be stored in silanized vial insert instead of pure glass vial type to reduce sample loss due to lipid extract adhering onto the glass surface, and to keep the extracts as fresh as possible at very low temperature (preferably at -80°C) [53].

Isoprostanoid extraction

Concentrations of isoprostanoids are low in biological samples therefore it is inevitable to extract the lipid in plasma and tissue samples prior to instrumental analysis. Conventionally, chloroform–methanol solvent systems such as Folch (chloroform/methanol, 2:1, v/v) or Bligh and Dyer (chloroform/methanol, 1:2, v/v) [48,57,58] is adopted. Thereafter, it is proceeded with a hydrolysis step as IsoPs are esterified to phospholipids [49,59]. Without hydrolysis, only free form of IsoPs is detectable in plasma and tissues, whereas after hydrolysis the total IsoPs (free+esterified) are measured. The hydrolysis are usually performed by the addition of high molar methanolic or ethanolic alkaline solution in an organic solvent (e.g. 1 M KOH in methanol) for 30 min at 37°C [60] or overnight in the dark, at room temperature [61]. In the metabolism, IsoPs are hydrolysed *in vivo* by phospholipase A₂ and the free IsoPs is excreted in the urine. However, the free IsoPs is suggested to form conjugates with glucuronide therefore, pre-treatment of the urine with glucuronidase is recommended to reduce the matrix effect and increase extraction efficiency [62]. It is also interesting to mention the use of methyl tert-butyl ether (MTBE). Extraction of some lipid species of major classes by MBTE was found to be the same or better than conventional chloroform–methanol solvent systems [63]. Compared to chloroform, MTBE is non-toxic, non-carcinogenic, non-corrosive, chemically stable and presents no danger of degrading labile lipids. Although it has not been tried for IsoPs extraction, it is worth investigating for its use in the future.

To specifically extract the isoprostanoids from plasma, tissues and urine, solid phase extraction (SPE) is commonly employed [49,64]. The type and packing of the sorbent, sample volume (with internal standard), composition and volume of the washing and elution solutions are parameters to consider when using SPE. Base on the affinity of isoprostanoids, specialized reversed phase sorbent [64] or ion-exchange (anionic, cationic, mixture of both) types are applied to clean and concentrate the compounds. Typically, weak anion exchange SPE are used for urine samples [65]. Another purification method is to combine SPE with thin layer chromatography (TLC) which is however, less reported due to high sample loss [47]. Other less frequently applied technique is the immunoaffinity chromatographic method that is used for 15-F_{2t}-IsoP analysis only, but not for ω -3 PUFAs derived isoprostanoids due to lack of specific immobilized antibodies [66]. Quehenberger and co-workers [67] developed a rapid method for high-throughput liquid–liquid extraction (LLE) which extracts a mixture of lipid mediators, including some free IsoPs in blood/plasma lipids, cultured cells, primary cells and animal tissues. The group used bi-phasic solution of acidified methanol and isoctane in the LLE.

More recently, León-Pérez et al. used a dispersive liquid–liquid microextraction (DLLME) followed by SPE clean-up to extract PhytoPs and PhytoFs from cocoa beans [68]. In other research, Domínguez-Perles et al. [56] mentioned for the first time, the use of bacteria and esterases derived from yeast for hydrolysis of PhytoPs and PhytoFs. The advantage of using enzymatic hydrolysis is the avoidance of unspecific reactions associated with alkaline hydrolysis that could lead to underestimation of the actual concentrations of these compounds in the analysed extracts. Another example is Peña-Bautista et al. [69] who developed and validated an analytical method for the quantification of IsoPs, IsoFs, NeuroPs and NeuroFs in human saliva. They used ultrasound-assisted liquid–liquid semi-microextraction (UA-LLsME), which is an advanced version of DLLME for the extraction.

Wittenberg and co-workers [70] used QuEChERS (Quick, Easy, Cheap, Efficient, Rugged and Safe) liquid–liquid extraction method for the sample preparation to analyse PG analogues in cosmetic products. It involves microscale extraction using acetonitrile solvent and dispersive SPE using a salt. The idea is based on partitioning of analytes of interest between two miscible liquids followed by phase separation by salting-out mechanism. The PG analogues are extracted in the upper organic phase. Based on this study, QuEChERS extraction method appeared to be affordable and worth further investigation in different sample matrices for isoprostanoids analysis. In a recent report, Biagini et al. [71] extracted 8-iso-PGE₂ (15-E₂-IsoP) from samples of dried red blood spots on specialized cards (Whatman™ Protein saver 903 cards) of newborn babies using micro-extraction and packed sorbent (MEPS) procedure, which is an advanced type of SPE. These reusable cartridges are highly sensitive and suited for small sample volume (10 μ l). Additionally, the group found the addition of isotopic internal standards on the card before blood spot sampling showed the method to be more reliable than adding during extraction process.

Analysis

Selecting a suitable analytical method is based on the expected goals, the budget and the availability of instrumentation. Generally, isoprostanoids analysis could be divided into immunological assays and mass spectrometry (MS) based techniques. Immunological techniques have the advantages to be time-saving and cost effective, especially when handling a large amount of sample size such as in human population studies [72]. However, to the best of our knowledge, commercial enzyme linked immunosorbent assay kits (ELISA kits) or radioimmunoassay kits (RIA

Kits) are specific for 15-F_{2t}-IsoP only. Moreover, cross-linking reaction can be observed with commercially available ELISA kits. Chromatography coupled to mass spectrometry (GC-MS, GC-MS/MS, LC-MS and LC-MS/MS) [73] are on the other hand, specific and sensitive, and allow quantification of particular metabolites found in low abundance in different sample matrices. In fact, both GC-MS/MS and LC-MS/MS is applicable for quantification of a wide range of isoprostanooids. In fact, Tsikas and Zoerner explicitly described in a comparative overview on the analysis of eicosanoids using GC-MS/MS and LC-MS/MS [74].

Nevertheless, a derivatization process is often required for GC-MS analysis to improve the volatility and thermal stability of the compounds. A well represented derivatization procedure of lipid extract is by converting the carboxylic acid into pentafluorobenzyl esters (PFB) by pentafluorobenzyl bromide (PFBBBr) in the presence of a catalyst such as N,N'-diisopropylethylamine. Thereafter, the hydroxyl groups are derivatized with either *O*-bis(trimethylsilyl)trifluoroacetamide +1% trimethylchlorosilane (BSTFA+TMCS) or *N*-Methyl-*N*-trimethylsilyltrifluoroacetamide [46,75] to form trimethylsilyl ether derivatives [75].

Derivatization is not necessary for LC-MS based isoprostanooid analysis, but available in some reports to increase the sensitivity of the analytes measured in positive electrospray ionization (ESI+). The strategy of the method is to use bromine labelled reagents for isotopic molecular pattern recognition [76,77]. A more recent study [78] showed that derivatization of PUFA metabolites with N-(4-aminomethylphenyl)-pyridinium resulted in a 10- to 30-fold increase in ionization efficiency. In contrast, Dupuy and co-workers [79] did not observe any improvement of ionization efficiency using derivatizing reagents, namely 2-hydrazinopyridine or 2-picolyamine. Regardless, analytical sensitivity was reported to be enhanced with picolyamine derivatives, but a unique picolyamine fragment ion of *m/z* 109 was also predominantly detected; this hindered the selection of specific daughter ion in the MS/MS for the measurement of isomeric IsoPs [80].

To date, no study could clearly prove the benefits of isoprostanooid derivatization prior LC-MS analysis. The reasons for this might be the additional steps needed, kinetic limitation due to the very low analyte concentrations, increased matrix effects caused by residual derivatization reagents as well as increased MS sensitivity in the negative mode ESI (ESI-) over the years, allowing the analysis of native isoprostanooids to be more specific. Altogether, derivatization process appears to benefit more in GC-MS and GC-MS/MS than LC-MS/MS measurements.

GC-MS and GC-MS/MS analysis

GC analysis is often a method of choice since it is ideally suited for the analysis of isoprostanooids due to its sensitivity and the absence of eddy diffusion [81]. Several ionization modes have been tried in GC-MS for the measurement of IsoPs. However, negative ion chemical ionization (NICI) mode, also referred to as electron-capture negative ionization, using methane as the reagent gas, is insofar the most reliable analytical setting to assess isoprostanooids. The derivatized PFB esters generate molecular ions that can be monitored either in selected-ion monitoring (SIM) or multiple-reaction monitoring (MRM) mode when using GC-MS/MS [82]. SIM mode is applied to monitor a single ion, e.g. *m/z* of 567 for F₃-IsoPs or *m/z* 593 for F₄-NeuroPs [31,64]. This can be disadvantageous as it cannot distinguish different isoprostanooid isomers since the single *m/z* is identical for the isomers and as a result, the measurement is considered the 'total' IsoPs, i.e. a sum of all the isomers and/or other metabolites. In turn, the MS/MS in MRM mode monitors the fragmented ions of the metabolites therefore increase the accuracy and selectivity [82–84]. Nonetheless, Tsikas and Suchy [85] improved the sample preparation by pre-extracting the IsoPs using immunoaffinity column chromatography for GC-MS and GC-MS/MS analysis. The protocol increased the purity and specificity of 15-F_{2t}-IsoP in the measurement of body fluids, especially those in low concentrations such as bronchoalveolar liquid and exhaled air condensate.

LC-MS and LC-MS/MS analysis

GC-MS method to some extent is sensitive, where vigorous extraction, and multiple derivatization steps are often required prior to instrumental analysis. These procedures can be avoided when using LC-MS or LC-MS/MS. Measurement of numerous isoprostanooids including the isomers in one sample makes LC-MS and LC-MS/MS spectrometry the preferred technique. Different ionization modes such as negative ESI or negative atmospheric pressure chemical ionization (APCI) [61,86] are applied in the analysis, but ESI- is the most frequently used. The analyser (triple quadrupole or quadrupole linear ion trap (QTrap)) allows SIM and/or MRM based analytical methods while a single MS detection method usually gives the exact masses of injected analytes over retention time. The MS/MS monitors the parent (precursor) ions Q1 and fragmented (daughter) ions Q3 of the molecule over retention time, therefore, MS/MS detection, enhance selectivity in detecting targeted metabolites, i.e. the position of hydroxyl function within the molecule [87]. An example is the detection of NeuroPs (4-F_{4t}-NeuroP and 10-F_{4t}-NeuroP series) where both compounds have the same precursor ion (Q1) *m/z* 377 but, after fragmentation, it produces unique mass transitions

(Q3), m/z 101 for 4-F_{4t}-NeuroP and m/z 153 for 10-F_{4t}-NeuroP [79]. The application of LC-MS/MS with precisely chosen MRM transitions is currently preferred as more informative results can be generated from a single sample and also, enable measurements of IsoPs from diverse series.

Non-aqueous microchip electrophoresis: a possible step towards the future of isoprostanoid analysis

Microchip electrophoresis (MC), a development from capillary electrophoresis, is considered a hybrid between electrophoresis and chromatography. It is a promising miniaturized platform with the potential to integrate many functions into a single device by 'lab-on-a-chip' concept [88]. Many advantages are reported concerning the use of MC including minute consumption of sample/reagent, high-throughput, cost-effectiveness and the possibility for portable analysis systems to be developed [89]. However, to the best of our knowledge, applications of MC in the field of targeted lipidomics remain very limited. Gibson and Bohn described a method to characterize lipids using non-aqueous MC and its potential application [90]. In this study, the separation of three model lipids depended on the voltage, the injection pulse timing, the concentration of background-electrolyte and the electric field strength. Separation of lipid mixtures was achieved with high resolution ($>5\times$) and high separation efficiency. This technique appears to be promising for the analysis of isoprostanoids and lipid peroxidation biomarkers.

Summary of recent analytical studies on isoprostanoids and isofuranoids

More recent analytical studies published for the quantifications of isoprostanoids and isofuranoids are presented in Tables 1 and 2. Notably, not all the isoprostanoids have been evaluated in biological specimens and analyses of PhytoPs are mainly conducted in food and plant samples (Table 2) whereas those of IsoPs and NeuroPs are mainly assessed in mammalian samples (Table 1). Evaluation of PhytoPs in mammalian tissues is still lacking, while PhytoFs have been quantitated for the first time in the liver tissue of rats supplemented with ALA-rich flaxseed [91].

Isoprostanoids as biomarkers in biological systems and potential bioactive molecules

The quantification of isoprostanoids can be performed in a variety of tissues and fluids, including most animal tissues, mammalian brain, cell lines, sputum, saliva and exhaled breath condensate (Table 1). The use of IsoPs as oxidative stress biomarkers has been expanded to the marine species where PUFA is dominantly found; these are also resources (e.g. oily fish and algae) of PUFA in the human diet. Recently, it was proposed that macroalgae could become the natural bio-resource for PhytoPs extraction instead of complex chemical syntheses [52]. In addition, isoprostanoids could become a potential signature for chemotaxonomy to discriminate macroalgae. Furthermore, plant oils are an important source of PUFAs in the diet, hence the use of PhytoPs as biomarkers of plant oil oxidation may fingerprint the oil quality [51,117] (Table 2).

In addition to isoprostanoid applications as oxidative stress biomarkers, they are reported to exert biological activities. They are homeostatic mediators and indispensable for important physiological functions such as inflammation and immune response.

Isoprostanones (IsoPs)

IsoPs as oxidative stress biomarkers

As previously mentioned, non-enzymatic lipid peroxidation is a metabolic process involved in many diseases such as cardiovascular diseases, neurological disorders, diabetes and renal dysfunction [8]. For years, reports focused on quantifying and/or assessing the levels of F₂-IsoPs, especially the most abundant 15-F_{2t}-IsoP, and to a smaller extent 5-F_{2t}-IsoP since they are ubiquitous and detected in a variety of biological samples including plasma, urine, lavage fluid and red blood cells. Increased level of F₂-IsoPs indicates the presence of oxidative stress injury. A recent meta-analysis of 242 distinct publications measuring the level of 15-F_{2t}-IsoP, ranked 50 different human health outcomes and related exposures. The study concluded that 15-F_{2t}-IsoP is the most promising biomarker to identify the aetiology or pathology of human diseases, and exposure to environmental contaminants [127]. Two years earlier from this report, the same main authors reinterpreted the *status quo* of 15-F_{2t}-IsoP to be the best biomarker of oxidative stress. By incorporating the fact that enantio-enriched 15-F_{2t}-IsoP can also be produced enzymatically with PGF_{2 α} (0.008 to 1 and 0.004 to 1 ratio depending on COX-1 or COX-2 respectively), the group clearly demonstrated that high production of 15-F_{2t}-IsoP by COX activities can mislead the meaning of 15-F_{2t}-IsoP as an oxidative stress biomarker [128,129]. Subsequently, the group introduced the use of 15-F_{2t}-IsoP /PGF_{2 α} ratio in the measurement of plasma samples to quantitatively distinguish the contribution of both chemical and enzymatic lipid peroxidation to the total

Table 1 Recent mammalian studies reported in relation to isoprostanoids and isofuranoids (since 2017)

Isoprostanoids and isofuranoids determined	Sample matrix	Analytical technique	Objective of the study	Ref.
PGs, IsoPs, dinor-IsoPs and IsoFs	Human plasma and urine	LC-MS/MS	Determination of ω -3/ ω -6 PUFAs ratios and the risk of developing exudative age-related macular degeneration (AMD).	[92]
PGs, hydroxy-DHA, IsoPs, dihom-IsoPs, NeuroPs, PhytoPs and IsoFs, dihom-IsoFs, NeuroFs	Neonatal mouse testis	LC-MS/MS	Identification of lipid mediators in mouse testes associated with in-utero perfluorooctane sulfonate (PFOS) exposure.	[61]
15- IsoPs and 5-IsoPs	Rat plasma	microLC-MS/MS	Study of calorie-dense obesogenic diet effect on obesity-related cardiovascular disease and lipid peroxidation.	[93]
IsoPs, PGs, NeuroPs and dihom-IsoFs	Human saliva	UPLC-MS/MS	Study of salivary lipid peroxidation products (non-invasive samples) as potential biomarkers of oxidative stress in neurodegeneration.	[69]
IsoPs, dihom-IsoPs, dihom-IsoFs, NeuroPs and NeuroFs	Human plasma	GC-MS and LC-Quadrupole Time-of-Flight (QTOF)-MS/MS	Garlic extract supplementation and health benefits to mild hypercholesterolemia.	[94]
IsoPs and IsoFs	Human plasma	LC-MS/MS	Development of an LC-MS/MS method for parallel quantification of 27 IsoPs and 8 IsoFs derived from 6 different PUFAs.	[54]
IsoPs and NeuroPs	Mouse plasma and kidney tissue	LC-MS/MS	Study on the effects of dietary ω -3 PUFAs supplementation on ischemia induced acute kidney injury in mice.	[95]
5-F ₂₁ -IsoP, 5-F ₃₁ -IsoP and 4-F ₄₁ -NeuroP	Human cell lines, <i>Caenorhabditis elegans</i> and murine kidney tissue	LC-MS/MS	Investigation about <i>trans</i> -epoxy-PUFAs and the <i>trans/cis</i> -epoxy-PUFAs ratio as potential new biomarker of lipid peroxidation.	[96]
IsoPs, dihom-IsoPs and NeuroPs	Mouse brain tissue	GC-MS/MS	Investigation on isoprostanoids formation in brain tissue of Krabbe disease mouse models.	[97]
4-F ₄₁ - and 10-F ₄₁ -NeuroPs	Plasma samples	GC-MS/MS	Identification and the clinical relevance of 4-F ₄₁ -NeuroP and 10-F ₄₁ -NeuroP in plasma of four different neurological diseases, including multiple sclerosis, autism spectrum disorders, Rett syndrome (RTT), and Down syndrome.	[42]
F ₂ -IsoPs and F ₄ -NeuroPs	Rabbit semen, blood samples and reproductive organs	GC-MS/MS	Dietary ω -3 PUFAs effect on reproductive traits using rabbit buck as an animal model.	[55]
IsoPs and PGs	Human urine	UPLC-MS/MS	Study on urinary biomarkers and inflammation status in athletes after an elite training period and supplementation of <i>Aronia</i> -citrus juice rich in polyphenols.	[98]
F ₃ - and F ₄ -NeuroPs and F ₂ -dihom-IsoPs	Human urine	UPLC-MS/MS	Measurement of excretory values of oxidative stress biomarkers in nervous system using healthy volunteers at different ages.	[99]
17-F _{2t} -dihom-IsoPs, 7-F _{2t} -dihom-IsoFs, 16-F _{1t} -PhytoPs and 16(RS)-13- <i>epi</i> ST Δ ^{14,9} -PhytoFs	Mouse liver and heart tissues	LC-MS/MS	Potential effects of oat bran in attenuating atherosclerosis in ApoE ^{-/-} mice.	[100]
15-F ₂₁ -IsoPs, and 5-F ₂ -IsoPs, 7-F ₂₁ -dihom-IsoPs, 17-F ₂₁ -dihom-IsoPs and 7-F ₂₁ - and 17-F ₂₁ -dihom-IsoFs	Acute retinal pigment epithelial cell	LC-MS/MS	Study of the potential roles of carotenoids and DHA by determining oxidized PUFAs products to evaluate potential contribution to AMD development.	[101]
5-F ₂₁ -IsoP, 15-F ₂₁ -IsoPs, IsoFs and NeuroFs	Human keratinocytes cells	LC-MS/MS	The effect of short-time ultraviolet A exposure on the aetiology of cell cycle and PUFAs lipid peroxidation.	[58]
F ₂ -dihom-IsoPs and NeuroPs	Human urine	UPLC-MS/MS	Study of the neuroprotection against oxidative stress after red wine consumption.	[102]
15-F ₁₁ -IsoP, 5- <i>epi</i> -15-F ₂₁ -IsoP, 15-F ₂₁ -IsoP, 5-F ₂₁ -5- <i>epi</i> -5-IsoP, 15-E ₁₁ -IsoP, 8 F ₃₁ -IsoP, 2,3-dinor-15-F ₂₁ -IsoP and 2,3-dinor-15- <i>epi</i> -IsoP	Human urine (females)	UPLC-MS/MS	Monitoring of systemic lipid peroxidation markers and enzymatic lipid oxidation in the human body related to the effect of the intake of red wine in female volunteers.	[103]
PhytoFs, IsoPs and NeuroPs	Mouse plasma	microLC-MS/MS	The effects of cyclic fatty acid monomers from heated vegetable oils on oxidative stress and inflammation.	[104]
IsoPs, dihom-IsoPs, NeuroPs NeuroFs, IsoFs and dihom-IsoFs	Preterm infants urine	LC-MS/MS	<i>In vivo</i> assessment of oxidative stress in urine samples from preterm infants fed with pasteurized human milk from donor and maternal milk.	[105]

Table 1 Recent mammalian studies reported in relation to isoprostanoids and isofuranoids (since 2017) (Continued)

Isoprostanoids and isofuranoids determined	Sample matrix	Analytical technique	Objective of the study	Ref.
15-F _{2t} -IsoP, 2,3-dinor-15- <i>epi</i> -15-F _{2t} -IsoP, 5-F _{2t} -IsoP, 15-keto-15-E _{2t} -IsoP, 15-E _{2t} -IsoP, 15-F _{2t} -IsoP, IsoFs, 10- <i>epi</i> -10-F _{4t} -NeuroP, d ₄ -10- <i>epi</i> -10-F _{4t} -NeuroP, 4(RS)-F _{4t} -NeuroP and PGs	Human urine	UPLC-MS/MS	Determination of new lipid peroxidation molecules to identify early Alzheimer's disease.	[106]
15-F _{2t} -IsoP, 2,3-dinor-15- <i>epi</i> -15-F _{2t} -IsoP, 5-F _{2t} -, 15-keto-15-E _{2t} -IsoP, 15-E _{2t} -IsoP, 15-F _{2t} -IsoP, IsoFs, 10- <i>epi</i> -10-F _{4t} -NeuroP, d ₄ -10-, <i>epi</i> -10-F _{4t} -NeuroP, 4(RS)-F _{4t} -NeuroP, NeuroFs and PGs	Human urine and plasma	UPLC-MS/MS	Determination of lipid peroxidation compounds in patients diagnosed with early Alzheimer's disease and development of artificial neural network for patients' classification.	[107]
15(R)-15-F _{2t} -IsoP, 2,3-dinor-15- <i>epi</i> -15-F _{2t} - IsoP, 5-F _{2t} -IsoP, 15, keto-15-E _{2t} -IsoP, 15-keto-15-IsoP, F _{2t} -IsoP, 15-E _{2t} -IsoP, 15-F _{2t} -IsoP, dihom-PGF _{2α} , PGE ₂ and PGF _{2α}	Human plasma	UPLC-MS/MS	Evaluation of lipid peroxidation compounds as early Alzheimer's disease biomarkers in plasma samples of patients' group.	[108]
15(R)-15-F _{2t} -IsoP, 2,3-dinor-15- <i>epi</i> -15-F _{2t} - IsoP, 5-F _{2t} -IsoP, 15-keto-15-E _{2t} -IsoP, 15-keto-15-IsoP, F _{2t} -IsoP, 15-E _{2t} -IsoP, 15-F _{2t} -IsoP, dihom-PGF _{2α} , dihom-IsoFs (7(RS)-ST-Δ ⁵ -11-series) PGE ₂ and PGF _{2α}	Human urine	HPLC-MS/MS	Evaluation of lipid peroxidation compounds as early Alzheimer's disease biomarkers in urine samples of patients' group.	[109]
4-F _{4t} -NeuroP, 4(RS)-4-F _{4t} -NeuroP, 10-F _{4t} -NeuroP, 5-F _{2t} -IsoP and 15-F _{2t} -IsoP	Rat plasma and tissues	LC-MS/MS	Evaluation of the potential bioactivities of 4-F _{4t} -NeuroP using a rat model and a neuronal cell line.	[40]
4- <i>epi</i> -4-F _{3t} -NeuroP _{n-6 DPA} , 4-F _{3t} -NeuroP _{n-6 DPA} , 4(RS)-F _{4t} -NeuroP, 4-F _{4t} -NeuroP, 10- <i>epi</i> -10-F _{4t} -NeuroP; 10-F _{4t} -NeuroP, d ₄ -4(RS)-F _{4t} -NeuroP, d ₄ -10- <i>epi</i> -10-F _{4t} -NeuroP, d ₄ -10-F _{4t} -NeuroP, 17- <i>epi</i> -17-F _{2t} -dihomo-IsoP, 17-F _{2t} -dihomo-IsoP, <i>ent</i> -7(RS)-7-F _{2t} -dihomo-IsoP, <i>ent</i> -7(S)-7-F _{2t} -dihomo-IsoP and 15-F _{2t} -IsoP	Human urine	UPLC-MS/MS	Study of possible applications of lipid peroxidation products in the evaluation of the allograft function after renal transplantation.	[110]
2,3-dinor-15-F _{2t} -IsoP, 2,3-dinor-15- <i>epi</i> -15-F _{2t} -IsoP, 5-F _{2t} -IsoP, 5- <i>epi</i> -5-F _{2t} -IsoP, 15- <i>epi</i> -15-E _{2t} -IsoP, 8-F _{3t} -IsoP, 15-keto-15-F _{2t} -IsoP and 8- <i>epi</i> -8-F _{3t} -IsoP	Human urine	UPLC-MS/MS	Investigation of several lipid peroxidation products as more accurate and predictive biomarkers of the allograft function after renal transplantation.	[111]
<i>ent</i> -9(RS)-12- <i>epi</i> -ST-Δ ¹⁴ -13-PhytoF and <i>ent</i> -16(RS)-9- <i>epi</i> -ST-Δ ¹⁴ -10-PhytoF	Rat liver tissue	LC-MS/MS	<i>In vivo</i> quantitation of phytofurans derived from ALA.	[91]
2,3-dinor-15-F _{2t} -IsoP, 15-keto-15-E _{2t} -IsoP, 15-keto-15-F _{2t} -IsoP, 15- <i>epi</i> -15-F _{2t} -IsoP, 15-E _{2t} -IsoP, 15-F _{2t} -IsoP, 5-F _{2t} -IsoP, 5- <i>epi</i> -5-F _{2t} -IsoP, 15- <i>epi</i> -2,3-dinor-15-F _{2t} -IsoP, 4-F _{4t} -NeuroP, 4- <i>epi</i> -4-F _{4t} -NeuroP, 10- <i>epi</i> -10-F _{4t} -NeuroP, 10-F _{4t} -, 14(RS)-14-F _{4t} -NeuroP, 4(RS)-ST-Δ ⁵ -8-NeuroP, 17(RS)-10- <i>epi</i> -SCΔ ¹⁵ -11-dihomo-IsoFs, 7(RS)-ST-Δ ⁸ -11-dihomo-IsoF, PGs and dihom-PG	Newborn plasma	UPLC-MS/MS	Development of analytical method for the determination of oxidative stress biomarkers in newborn plasma.	[112]
15-F _{2t} -IsoP	Human urine	ELISA kit	Evaluating the prevalence of urinary 15-F _{2t} -IsoP and peroxidation of lipids induced by wood dust exposure.	[113]
F ₂ -IsoP metabolite	Human urine	GC-MS	Determination of the relation between exposure to airborne fine particulate matter and oxidative stress biomarkers and inflammation.	[114]
15-F _{2t} -IsoP	Dairy cattle, plasma, urine and milk	LC-MS/MS and ELISA	Study compared oxidant status of healthy dairy cow and those lactating with acute coliform metastasis.	[115]
15-F _{2t} -IsoP	Human urine	ELISA kit	Examined the association of urinary 15-F _{2t} -IsoP with all cause in dementia, Alzheimer's disease and vascular dementia.	[72]
8-isoPGF _{2α} , 8-isoPGE ₂ and PGE ₂	Dried blood spots of newborns	UPLC-MS/MS	Method development using semi-automated micro-extraction by packed sorbent (MEPS) clean-up for the measurement of prostanoids and IsoPs in dried blood spots from new born babies.	[71]

Abbreviations: ELISA, enzyme-linked immunosorbent assay; GC, gas chromatography; HPLC, high-performance liquid chromatography; IsoF, isofuran; IsoP, isoprostane; LC, liquid chromatography; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NeuroF, neurofuran; NeuroP, neuroprostane; PG, prostaglandin; PhytoF, phytofuran; PhytoP, phytoprostane; UPLC, ultra-performance liquid chromatography.

Table 2 Recent studies reported on isoprostanoids and isofuranoids related to plants and food (since 2017)

Isoprostanoids and isofuranoids determined	Sample matrix	Analytical technique	Objective of the study	Ref.
PhytoPs, PhytoFs, IsoPs and NeuroPs	Marine red and brown macroalgae	microLC-MS/MS	Understanding the importance of isoprostanoids in seaweeds, brown (Phaeophyta) and red (Rhodophyta) macroalgae.	[52]
5-F ₂₁ -IsoP, 15-F ₂₁ -IsoP and 4-F ₃₁ -IsoP	Salmon filets (with skin)	GC-MS and LC-MS/MS	Effect of high temperature cooking of fish (salmon) and different condiments on potential degradation of ω -3 fatty acids.	[57]
PhytoPs and PhytoFs	Coffee pulp, cocoa husk and pod husk	microLC-MS/MS	Quantification of PhytoPs and PhytoFs in coffee and cocoa.	[116]
16-F ₁₁ -PhytoP, 9-F ₁₁ -PhytoP and 9-D ₁₁ -PhytoP	Extra virgin olive oil	UPLC-MS/MS and GC-MS/MS	Study of the effect of the contents of extra virgin olive oil on four enzymes: α -glucosidase, α -amylase, acetylcholinesterase and butyrylcholinesterase.	[117]
PhytoPs and PhytoFs	Legume Foods	UPLC-MS/MS	Study of the relevance of sustained deficit irrigation on the occurrence of PhytoPs and PhytoFs in three dietary legume species.	[118]
PhytoPs and PhytoFs	Cocoa beans samples	UPLC-MS/MS	Assessment of PhytoPs and PhytoFs concentrations in cocoa bean from different clones.	[68]
15-F ₂₁ -IsoP, 5-F ₂₁ -IsoP, 5-F ₃₁ -IsoP, 8-F ₃₁ -IsoP, 15-F ₃₁ -IsoP, 7-F ₂₁ -dihomo-IsoP, 17-F ₂₁ -dihomo-IsoP, 4-(RS)-4-F ₄₁ -NeuroP, 10-F ₄₁ -NeuroP and 7-F ₂₁ -IsoF and 17-F ₂₁ -dihomo-IsoF	Salmon filets	LC-MS/MS	Study on the effect of cooking methods on the quality of PUFAs in fatty fish (salmon).	[48]
16-F ₁₁ -PhytoP, 9-F ₁₁ -PhytoP, 16-E ₁₁ -PhytoP, 9-D ₁₁ -PhytoP and PhytoFs	Pollen grains	LC/MS	Chemical analyses of pollen associated lipids that are rapidly released upon hydration.	[119]
9-F ₁₁ -PhytoP, 9- <i>epi</i> -9-F ₁₁ -PhytoP, <i>ent</i> -16-F ₁₁ -PhytoP, <i>ent</i> -16- <i>epi</i> -16-F ₁₁ -PhytoP, <i>ent</i> -9-D ₁₁ -PhytoP, <i>ent</i> -9- <i>epi</i> -9-D ₁₁ -PhytoP, 16-B ₁ -PhytoP, 9-L ₁ -PhytoP, <i>ent</i> -16-(RS)-9- <i>epi</i> -ST- Δ^{14} -10-PhytoF, <i>ent</i> -9-(RS)-12- <i>epi</i> -ST- Δ^{10} -13-PhytoF and <i>ent</i> -16-(RS)-13- <i>epi</i> -ST- Δ^{14} -9-PhytoF	Roasted hazelnut	UPLC- MS	Assessment of the fatty acid, oxylipin and phenolic composition roasted hazelnut snacks.	[120]
PhytoPs (9-F ₁₁ -PhytoP, 9- <i>epi</i> -9-F ₁₁ -, <i>ent</i> -16-F ₁₁ -, <i>ent</i> -16- <i>epi</i> -16-F ₁₁ -, 9-D ₁₁ -, 9- <i>epi</i> -9-D ₁₁ -, 16-B ₁ -9-L ₁ -series) and PhytoFs (<i>ent</i> -16-(RS)-9- <i>epi</i> -ST- Δ^{14} -10-, <i>ent</i> -9-(RS)-12- <i>epi</i> -ST- Δ^{10} -13- and <i>ent</i> -16-(RS)-13- <i>epi</i> -ST- Δ^{14} -9-series)	Vegetable oil	UPLC- MS/MS	Profiling and quantification of PhytoPs and PhytoFs in vegetable oils.	[51]
PhytoPs (9-F ₁₁ -, 9- <i>epi</i> -9-F ₁₁ -, <i>ent</i> -16-115 F ₁₁ -, <i>ent</i> -16- <i>epi</i> -16-F ₁₁ -, <i>ent</i> -9-D ₁₁ -, <i>ent</i> -9- <i>epi</i> -9-D ₁₁ -, 16-B ₁ -, 9-L ₁ -series) and PhytoFs (<i>ent</i> -16-(RS)-9- <i>epi</i> -ST- Δ^{14} -10-, <i>ent</i> -9-(RS)-12- <i>epi</i> -ST- Δ^{10} -117 13- and <i>ent</i> -16-(RS)-13- <i>epi</i> -ST- Δ^{14} -9-series)	Pea seeds	UPLC-MS/MS	Optimization the conditions needed for efficient enzymatic hydrolysis of PhytoP and PhytoF esters.	[56]
PhytoPs (9-F ₁₁ -, 9- <i>epi</i> -9-F ₁₁ -, <i>ent</i> -16-F ₁₁ -, <i>ent</i> -16- <i>epi</i> -16-F ₁₁ -, 9-D ₁₁ -, 9- <i>epi</i> -9-D ₁₁ -, 16-B ₁ -, <i>ent</i> -16-B ₁ -9-L ₁ - and <i>ent</i> -9-L ₁ -series)	Banana passion fruit	LC-MS	Detection of bioactive compounds in banana passion fruit shell for biological activities in humans.	[121]
PhytoPs (9-F ₁₁ -, <i>ent</i> -16-F ₁₁ -, <i>ent</i> -16- <i>epi</i> -16-F ₁₁ -, 9- <i>epi</i> -9-F ₁₁ -, 9- <i>epi</i> -9-D ₁₁ -, 9-D ₁₁ -PhytoP, 16-B ₁ -, <i>ent</i> -16-B ₁ -9-L ₁ - and <i>ent</i> -9-L ₁ -series)	Physalis peruviana calyces	UPLC-MS/MS	Detection method of PhytoPs in <i>Physalis peruviana</i> calyces.	[122]
PhytoPs (9-F ₁₁ -, <i>ent</i> -16-F ₁₁ -, <i>ent</i> -16- <i>epi</i> -16-F ₁₁ -Phyt, 9-D ₁₁ -, 9- <i>epi</i> -9-D ₁₁ -, 16-B ₁ -, 9-L ₁ -series) and PhytoFs (<i>ent</i> -16(RS)-9- <i>epi</i> ST- Δ^{14} -10-, <i>ent</i> -9(RS)-12- <i>epi</i> -ST- Δ^{10} -13- and <i>ent</i> -16(RS)-13- <i>epi</i> -ST- Δ^{14} -9 series)	Rice flours	UPLC-MS/MS	Study on the effects of salicylic acid supplementation on rice genotypes from <i>Oryza sativa</i> L.	[123]
PhytoPs (<i>ent</i> -16- <i>epi</i> -16-F ₁₁ -, 9-F ₁₁ -, <i>ent</i> -16-F ₁₁ -, 9- <i>epi</i> -9-F ₁₁ -, <i>ent</i> -9-D ₁₁ -, <i>ent</i> -9- <i>epi</i> -9-D ₁₁ -, 16-B ₁ -, 9-L ₁ -series) and PhytoFs (<i>ent</i> -9-(RS)-12- <i>epi</i> -ST- Δ^{10} -13-, <i>ent</i> -16-(RS)-9- <i>epi</i> -ST- Δ^{14} -10- and <i>ent</i> -16-(RS)-13- <i>epi</i> -ST- Δ^{14} -9-series)	Dried rice grains	UPLC-MS/MS	Determination on effects of foliar fertilization on the concentration of PhytoPs and PhytoFs and its impact on the yield and the quality of rice.	[124]
PhytoPs (9-F ₁₁ -, <i>ent</i> -16-F ₁₁ -, <i>ent</i> -16- <i>epi</i> -16-F ₁₁ -, 9- <i>epi</i> -9-F ₁₁ -9-, D ₁₁ -9- <i>epi</i> -9-D ₁₁ -, <i>ent</i> -16-B ₁ -, 16-B ₁ -, <i>ent</i> -9-L ₁ -PhytoP, 9-L ₁ -series) and PhytoFs (<i>ent</i> -16-(RS)-9- <i>epi</i> -ST- Δ^{14} -10-, <i>ent</i> -9-(RS)-12- <i>epi</i> -ST- Δ^{10} -13- and <i>ent</i> -16-(RS)-13- <i>epi</i> -ST- Δ^{14} -9 series)	Rice flours and brans	UPLC -MS/MS	Profiling the concentration of PhytoPs and PhytoFs in white and brown grain flours and rice bran from 14 rice cultivars of the <i>indica</i> and <i>japonica</i> subspecies.	[125]

Table 2 Recent studies reported on isoprostanoids and isofuranoids related to plants and food (since 2017) (Continued)

Isoprostanoids and isofuranoids determined	Sample matrix	Analytical technique	Objective of the study	Ref.
F ₂ -isoPs	Fish skin mucus samples	HPLC-MS/MS	Development and optimization of a HPLC-MS/MS method to quantify F ₂ -IsoP isomers in fish mucus.	[126]

Abbreviations: ELISA, enzyme-linked immunosorbent assay; GC, gas chromatography; HPLC, high-performance liquid chromatography; IsoF, isofuran; IsoP, isoprostane; LC, liquid chromatography; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NeuroF, neurofuran; NeuroP, neuroprostane; PG, prostaglandin; PhytoF, phytofuran; PhytoP, phytoprostane; UPLC, ultra-performance liquid chromatography.

measurement of 8-iso-PGF_{2α} level. However, this ratio is applicable only for 'free' 15-F_{2t}-IsoP level in the plasma that constitutes approximately 5-10% of the 'total' 15-F_{2t}-IsoP (free + esterified) levels. Therefore, one can infer the 'total' to represent entirely non-enzymatic oxidative damage in *in vivo* studies when viewing the concentration and ratio weighting of 'total' compared to 'free' 15-F_{2t}-IsoP amount [130].

Lately, this new ratio was applied in urine samples [131,132]. However, the authors of the study had concerns about the usefulness of the 15-F_{2t}-IsoP /PGF_{2α} ratio in urine following the precedent work by Morrow and co-workers [133]. They clearly showed that quantification of urinary PGF_{2α} actually reflects oxidative stress status as oppose to COX activity because the only PGF_{2α} that is measurable in urine is the other enantiomer that is formed via non-enzymatic peroxidation. Therefore, it seems more problematic to use this 15-F_{2t}-IsoP /PGF_{2α} ratio in urine samples.

IsoPs were recently found to be potential biomarkers in age-related macular degeneration (AMD) in Chinese adults. This is an ocular disease and the principal cause of visual impairment in most developed countries [92,101,134]. In addition, the group [101] also evaluated the impact of carotenoids and DHA supplementation on acute retinal pigment epithelial (RPE) cells under oxidative stress. The authors found that treatment with carotenoids (e.g. lutein, zeaxanthin) lowered 5-F_{2t}-IsoP, 15-F_{2t}-IsoP and 4-F_{3t}-IsoP levels while the addition of DHA did not further reduce these effects.

A significant relationship between physical exercises, F₂-IsoPs levels and inflammation biomarkers in triathletes was proposed by García-Flores et al. [98]. Intake of antioxidant-rich beverage containing polyphenols stimulated the excretion of some metabolites related to vascular and smooth muscle function, e.g. 15-epi-15-E_{2t}-IsoPs and 15-keto-F_{2t}-IsoP, indicating its potential role in enhancing cardiovascular health in athletes. Nonetheless, a different effect was observed for garlic extract, which is also rich in antioxidant polyphenol in mild hypercholesterolemia [94]. Surprisingly, 15-F_{2t}-IsoP concentration was not altered by the extract intake and in fact, the benefits observed were related to plasma ALA enrichment and AA-lipoxygenase inhibition.

Another report noted an increase of 15-F_{2t}-IsoP in urine of industrial workers exposed to carcinogenic wood dust [113]. It was also shown [114] that fine particles (PM_{2.5}, 0.1–2.5 μm in diameter) in air pollution leads to oxidative stress *in vivo* where a correlation between exposure to airborne PM_{2.5} and urinary F₂-IsoP levels was observed.

Levels of 15-F_{2t}-IsoP was evaluated in plasma, urine and milk of healthy dairy cattle and lactating cattle with acute coliform mastitis. During acute coliform mastitis, excessive production of ROS by phagocytic cells leads to oxidative damage in the mammary tissue of the dairy cattle; both plasma and urine 15-F_{2t}-IsoP were elevated in the cattle suffering from mastitis [115].

More recent reports suggest that IsoPs and IsoFs could be potential Alzheimer's disease biomarkers at mild dementia phase [72,106]. In a large population study that had 14 years follow-up showed low physical activity and diabetes were associated with dementia incidence and elevated urinary 15-F_{2t}-IsoP levels. Furthermore, in the study, urinary 15-F_{2t}-IsoP levels were related to all-cause dementia incidence and Alzheimer's disease [72]. This was further verified when investigated in different statistical models [107,109] such as artificial neural network, non-linear partial least square, elastic-net-penalized regression and support vector machine that included different variables such as gender, age, smoking and alcohol consumption.

The brain white matter is rich in AdA. Recent findings indicate AdA-derived F₂-dihomo-IsoPs to be potential oxidative stress biomarkers for neurological diseases related to the white matter. Significantly high levels of plasma F₂-dihomo-IsoPs and urinary 7-F_{2t}-dihomo-IsoPs in patients with neurological disorders, such as RTT were observed [135]. In addition, urinary dihom-IsoPs was found to increase in epileptic patients compared with healthy individuals [136] and an elevation in plasma and urine increased the risk of developing wet AMD [92].

F₂-IsoPs recently received a great attention in marine science, especially for conservation reasons. A non-invasive method for quantification of F₂-IsoPs in fish mucus was developed to monitor the health status, i.e. by oxidative stress level of wild trout, and to understand the interspecies variation [126].

Although F_{2t}-IsoPs arise from PUFA peroxidation, insofar, not many investigations on food is reported; in particular lipid peroxidation induced by heat is mainly initiated by free radical. Indeed, pan-frying and oven-baking salmon fish presented high concentrations of 5-F_{2t}-IsoP and 15-F_{2t}-IsoPs compared to raw ones [48]; however, it was not reduced when antioxidant herb condiments were added to salmon during pan frying [57].

Biological activities of IsoPs

As already mentioned, 15-F_{2t}-IsoP was found to be a vasoconstrictor and many reports observed the constrictive effect in the liver, heart, lung, smooth muscle, retina, peripheral lymphatic and airway, and also renal systems at low nanomolar levels [3,137–139]. The compound can potentially be used as a reliable vasoconstrictor in cardiovascular diseases [14]. This biological effect is related to an agonist/antagonist effects by activating or inhibiting thromboxane receptors (TPR) depending on the binding site [140,141]. The binding mechanism of 15-F_{2t}-IsoP for the active site of the platelet TPRs revealed a unique coordination that requires an additional interaction with Phe¹⁹⁶ [142]. The second binding site of 15-F_{2t}-IsoP of platelet was found via an unknown cyclic adenosine monophosphate-coupled receptor that inhibits the platelet activation [142].

More recently, 15-F_{2t}-IsoP was found to affect mouse bone marrow macrophage adhesions and migration, where an integral component of macrophage were involved in the atherosclerosis stimulating colony stimulating factor-1 pathway [143]. Not all F₂-IsoPs present the same biological activities and some effect seem to be specific for particular compounds or series. For example, 15-F_{2c}-IsoP activated the PGF_{2α} receptor causing hypertrophy of cardiomyocytes via intracellular signalling pathways different from those of PGF_{2α} [144,145]. Another example is the 5-F_{2t}-IsoP which showed no vasomotor activity [146,147]. Moreover, E-series IsoPs such as 15-E_{2t}-IsoP displayed renal vasoconstrictive effect and was even more potent than 15-F_{2t}-IsoP in activation of thromboxane-prostanoid and prostaglandin E₃ receptors [148,149]. Other biological activities of 15-E_{2t}-IsoP include activation of intestinal epithelial cell contraction, stimulation of monocyte endothelial cells binding, gastrointestinal smooth muscle contraction and regulator of the airways [150–154]. The analogous 15-D₂-IsoP is less investigated as it is rather unstable [155] and similarly, 15-E_{2t}-IsoP is subjected to dehydration to form the cyclopentenone J₂- and A₂-series, respectively (see section '*In vivo* formation of isoprostanoids (biosynthesis)'). 15-J₂-IsoP was found to have inflammatory response by inhibiting via the peroxisome proliferator-activated receptor gamma (PPARγ) activation and induce RAW264.7 cell apoptosis in a PPARγ-independent manner [156]. In turn, anti-inflammatory effects of 15-A₂-IsoP was also reported by the inhibition of nuclear factor-kappaB (NF-κB) pathway in lipopolysaccharide (LPS)-induced macrophages and human gestational tissues [156,157].

On the other hand, F₃-IsoPs derived from EPA present anti-inflammatory and anti-thrombotic activities by lowering the production of pro-inflammatory PGs and thromboxanes derived from AA [48]. However, 5-F_{3t}-IsoPs was found to modulate the release of neurotransmitters in isolated bovine retina [158]. Another report showed that 15-A_{3t}-IsoP has anti-inflammatory effects on LPS-stimulated macrophages via the inhibition of NF-κB pathways, and inhibitory effect on the formation of foam cells, a major step in the pathogenesis of atherosclerosis [159].

Phytoprostanes (PhytoPs)

PhytoPs as oxidative stress biomarkers

PhytoPs are isoprostanoids produced by the action of ROS on ALA in plants. Mammals do not endogenously produce ALA due to the lack of delta-12 and delta-15 desaturase enzymes, which are needed for the synthesis of essential fatty acids from mono-unsaturated fatty acids. Many different PhytoPs have been identified, including E₁-, B₁-, D₁-, A₁- and L₁-PhytoPs [13,160]. It is noted that A₁-series is readily isomerized into B₁-series under extreme pH or high temperature. However, both A₁- and B₁-PhytoPs are produced in low abundance in plants, while D₁- and F₁-PhytoPs are the most abundant [161]. PhytoP profiles and levels in plants have recently been found to be affected by various agricultural practices. Thus, it is perceived PhytoPs to be excellent biomarkers for oxidative degradation of plant food.

PhytoPs and PhytoFs were determined in crops to unveil the oxidative response to irrigation deficit, and also to evaluate their importance as functional food [118]. A recent study [123] investigated the interrelation of the farming practice, i.e. open field and plastic cover, and spraying of salicylic acid on rice flour with the concentration of PhytoPs where a decrease in most PhytoP levels was observed. Furthermore, the concentration of PhytoPs and PhytoFs decreased in brown rice flour produced by foliar fertilization [124] while the average PhytoP concentrations were higher in rice bran flour than in white and brown grain flours [125].

In a different study [162], PhytoPs in three types of nuts (macadamia, pecan and walnut) were characterized and monitored in the treatment process that influence the final quality of nuts. Interestingly, heat treatment, i.e. frying augmented the PhytoP concentrations in these nuts.

Recently, Vigor and co-workers [52] investigated isoprostanoids including PhytoPs, PhytoFs and IsoPs in brown (*Phaeophyta*) and red (*Rhodophyta*) macroalgae after heavy metal (copper) exposure. They found that *ent*-16(*RS*)-9-*epi*-ST- Δ^{14} -10-PhytoF and 5-F_{2t}-IsoP were the most abundant oxidized PUFA metabolites in these macroalgae, suggesting its potential use in chemotaxonomy to discriminate between macroalgae species under environmental contaminants.

Several researches have been oriented towards green technology of industrial food waste to find further use of such waste. In this context, recent studies [68,116] identified PhytoPs and PhytoFs in coffee pulp, cocoa husk and pod husk residues and suggest to be valuable natural resources of PhytoPs and PhytoFs instead of chemically synthesizing them. Furthermore, Medina and co-workers [121,122,163] investigated the possible use of banana passion fruit shell waste as well as other tropical fruits (e.g. *Passiflora edulis* and *Physalis peruviana*) as natural sources of bioactive compounds including PhytoPs.

Biological activities of PhytoPs

In addition to their application as biomarkers of oxidative stress in plants, very little is known in human health benefits. *In vitro* study showed that B₁-PhytoPs were neuroprotective for undifferentiated, but not differentiated, SH-SY5Y cells from H₂O₂ insult, and promoted oligodendrocyte differentiation partly via PPAR γ activation [13]. Moreover, PhytoPs could be involved in anti-inflammatory and apoptosis inducing activities, especially A₁-PhytoPs and to lesser extent B₁-PhytoPs in Jurkat T-cells [12,14]. The mechanism for such action indeed was similar to the well-known prostaglandin A.

Extra virgin olive oil is considered the primary source of dietary fat in the Mediterranean diet. A recent work [117] reported potential health benefits and hypoglycaemic effects of extra virgin olive due to the inhibition of α -glucosidase and α -amylase enzyme activities. The group suggested that the high PhytoPs in the oil may be responsible for this. As this was an *in vitro* investigation, further studies are needed to confirm the potential effect of PhytoPs and PhytoFs *in vivo* by comparing structure-activity relationship with other bioactive prostanoids particularly human oxylipins [164].

Neuroprostanes (NeuroPs)

NeuroPs as oxidative stress biomarkers

NeuroPs formation is achieved via free-radical mediated peroxidation of DHA [31]. DHA is the most abundant ω -3 PUFA in humans and highly enriched in several tissues including the cerebral cortex and retina. F₄-NeuroPs are widely used as biomarkers for oxidative damage related to the central nervous system [40]. Due to its high abundance, particularly in grey matter of the brain, elevation of F₄-NeuroPs, especially 4-F_{4t}-NeuroP is considered a exclusive indicator for neuronal oxidative damage [42,45]. Among all the F₄-NeuroPs, 4-F_{4t}-NeuroP and 10-F_{4t}-NeuroP are the most represented in neuropathological conditions [14].

In most times, F₂-IsoPs are investigated together with F₄-NeuroPs in studies related to oxidative stress biomarkers of neuronal diseases, to clarify the role of oxidative damage in the pathogenesis such as in Parkinson's disease [165]. Altered levels of F₄-NeuroPs in plasma were also found in RTT [84], while increased plasma and urinary F_{4t}-NeuroPs were associated with risk of wet AMD in Chinese adults [92]. Aside from these, other PUFA peroxidation products related to the brain include IsoFs, NeuroFs, F₂-dihomo-IsoPs and dihom-IsoFs, were investigated as potential biomarkers in the pathogenesis of Alzheimer's disease [106,109].

Recently, F_{3t}-NeuroP_{n-6} a metabolite of DPA and F_{2t}-dihomo-IsoPs were found useful to assess renal function after kidney transplantation [110,111]. The authors noted that these three metabolites namely, 4-*epi*-4-F_{3t}-NeuroP_{n-6} DPA, *ent*-7(*RS*)-7-F_{2t}-dihomo-IsoP and *ent*-7(*S*)-7-F_{2t}-dihomo-IsoP tended to decrease when kidney function improved and the excretion of urine proteins decreased.

Biological activities of NeuroPs

NeuroPs are not merely biomarkers but also bioactive molecules. The first study on NeuroP bioactivities have been performed by Musiek and co-workers and described 14-A₄-NeuroP as a potent anti-inflammatory mediator, inhibiting NF- κ B activation in LPS-induced macrophages [166]. Similarly, Majkova et al. showed that A₄/J₄-NeuroPs, derived from DHA, down-regulated PCB77-induced monocyte chemo-attractant protein-1 expression and nuclear factor erythroid 2-related factor 2 (Nrf2) activation in primary pulmonary endothelial cells [167]. Moreover, 4-(*RS*)-4-F_{4t}-NeuroP displayed particularly interesting antiarrhythmic properties both *in vivo* and *in*

vitro via the protection of ryanodine receptor [11], and also protected against ventilator-induced diaphragmatic dysfunction (VIDD) in a similar manner [168]. It was also shown that 4-(*RS*)-4- F_{4t} -NeuroP protected against ischemia-reperfusion damages in mice [10,11].

In other observations, both 4-(*RS*)-4- F_{4t} -NeuroP and 14- A_{4t} -NeuroP displayed anti-inflammatory activities similar to the protectins in human macrophages [169]. Moreover, 4-(*RS*)-4- F_{4t} -NeuroP showed anticarcinogenic activities by limiting the proliferation of carcinogenic cells in human breast cancer [170]. In a more recent report [40], 4-(*RS*)-4- F_{4t} -NeuroP was found to mediate anti-inflammatory hydroxy-DHA in rat liver and brain, and augmented hemoxygenase-1 gene expression. The group further showed that under extreme oxidative stress environment, 4-(*RS*)-4- F_{4t} -NeuroP may potentially oxidize to toxic aldehydes in neuroblastoma cells. As a consequence, low NeuroPs and high PUFA aldehydes in circulation is suggested to be contributors in AMD development [92].

Conclusions and future visions

As of today, in the study of isoprostanoids, efforts are focused on understanding their hidden mode of actions in humans or plants. Current discovery related to the DHA derivatives (NeuroPs) clearly will advance our knowledge in human pathologies related to neurodegeneration and the role of essential PUFAs in our diet. In recent years, measurement of isoprostanoids is emerging in agriculture and marine science, especially studies related to environmental contaminants and sustainability in the food chain. This is necessary for quality assurance of essential PUFA resources for human nutrition.

Here, we updated and explored recent literatures related to biochemistry, analytical chemistry and biology of isoprostanoids generated from main ω -6 and ω -3 PUFAs in the last few years. It is affirmed that these oxygenated metabolites not only serve as oxidative stress biomarkers in many diseases, but also contribute to health, environmental and industrial benefits.

Finally, the ongoing progress in the availability and synthesis of pure standards as well as the use of robust and sensitive analytical methodologies such as LC-MS/MS and GC-MS/MS instrumentations now allow easier profiling of new biomarkers of oxidative stress in different biological matrices. Yet, development of novel analytical techniques such as microchip electrophoresis is currently in progress.

Summary

- The present paper describes the recent updates from 2017 until now on isoprostanoids.
- These isoprostanoids are not only considered biomarkers of oxidative damage, but also display a broad range of biological activities in human body.
- Conceptual progress in research concerning these isoprostanoids has added more understanding about their importance in different fields.
- The objective of this chapter is to give a scope over these isoprostanoids including their biological activities, their biosynthesis pathways and to summarize recent developed analytical approaches for them.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations

AA, arachidonic acid; AdA, adrenic acid; ALA, α -linolenic acid; AMD, age-related macular degeneration; APCI, atmospheric pressure chemical ionization; BHT, butylated hydroxytoluene; BSTFA, *bis*-(trimethylsilyl)trifluoroacetamide; COX, cyclooxygenase enzymes; DHA, docosahexaenoic acid; DTPA, diethylene tri-amine pentaacetic acid; ELISA, enzyme-linked immunosorbent assay; EPA, eicosapentaenoic acid; ESI, electrospray ionization; GC-MS, gas chromatography mass spectrometry; GSH, glutathione; IsoP, isoprostane; LC-MS, liquid chromatography mass spectrometry; LLE, liquid-liquid extraction; LPS, lipopolysaccharide; MC, microchip electrophoresis; MEPS, micro-extraction by packed sorbent; MRM, multiple-reaction monitoring; MS/MS, tandem mass spectrometry; MTBE, methyl-*tert*-butyl ether; NeuroP, neuroprostane; NF- κ B, nuclear

factor-kappaB; NICl, negative ion chemical ionization; Nrf2, nuclear factor erythroid 2-related factor 2; PA, picolylamine; PAF, platelet activating factor; PFBBr, pentafluorobenzyl bromide; PFOS, perfluorooctane sulfonate; PG, prostaglandin; PhytoF, phytofuran; PhytoP, phytostane; PUFA, polyunsaturated fatty acid; QTOF, quadrupole time-of-flight; QuEChERS, Quick, Easy, Cheap, Efficient, Rugged and Safe; RIA, radioimmunoassay; ROS, reactive oxygen species; RTT, Rett syndrome; SIM, selected-ion monitoring; SPE, solid phase extraction; TLC, thin layer chromatography; TPP, triphenylphosphine; TPR, thromboxane receptor.

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