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Isoprostanes, neuroprostanes and phytoprostanes: An overview of 25 years of research in chemistry and biology

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A B S T R A C T

Since the beginning of the 1990's diverse types of metabolites originating from polyunsaturated fatty acids, formed under autooxidative conditions were discovered. Known as prostaglandin isomers (or isoprostanoids) originating from arachidonic acid, neuroprostanes from docosahexaenoic acid, and phytoprostanes from α -linolenic acid proved to be prevalent in biology. The syntheses of these compounds by organic chemists and the development of sophisticated mass spectrometry methods has boosted our understanding of the isoprostanoid biology. In recent years, it has become accepted that these molecules not only serve as markers of oxidative damage but also exhibit a wide range of bioactivities. In addition, isoprostanoids have emerged as indicators of oxidative stress in humans and their environment. This review explores in detail the isoprostanoid chemistry and biology that has been achieved in the past three decades.

1. Introduction

The discovery of isoprostanes (IsoPs) nearly three decades ago as biomarker of oxidative stress [1] opened a new field of research in arachidonic acid (AA) and its eicosanoid metabolism. Today, it is accepted that IsoPs are more than only biomarkers and bystanders of physiological processes. IsoPs have been shown to act as lipid mediators in vasoconstriction and platelet aggregation, and may participate in intracellular signaling through the activation of prostanoid receptors [2]. Unlike the prostaglandins (PGs), IsoP biosynthesis is not dependent on the cyclooxygenase enzyme, instead it is propagated by free radical reactions, mainly driven by reactive oxygen species (ROS). Presently, it is well accepted that IsoP generation takes place *in situ* by the reaction of ROS with glycerophospholipids, mainly phosphatidylcholine. The esterified IsoPs can be released from the phospholipid by the action of phospholipase A₂ and platelet activating factor acetylhydrolase. While

a plethora of isomeric IsoPs have been described, undoubtedly 15-F_{2t}-Isoprostane (15-F_{2t}-IsoP) is the predominant one investigated. Once released into the circulation, the free 15-F_{2t}-IsoP is β -oxidized to form an intermediate compound, 2,3-dinor-15-F_{2t}-IsoP that can further undergo reduction to 2,3-dinor-5,6-dihydro-15-F_{2t}-IsoP for urinary excretion [3]. However, an alternative β -oxidation processes takes place in rodents to produce 2,3,4,5-tetranor-15-F_{2t}-IsoP (Section 2.2) [4,5].

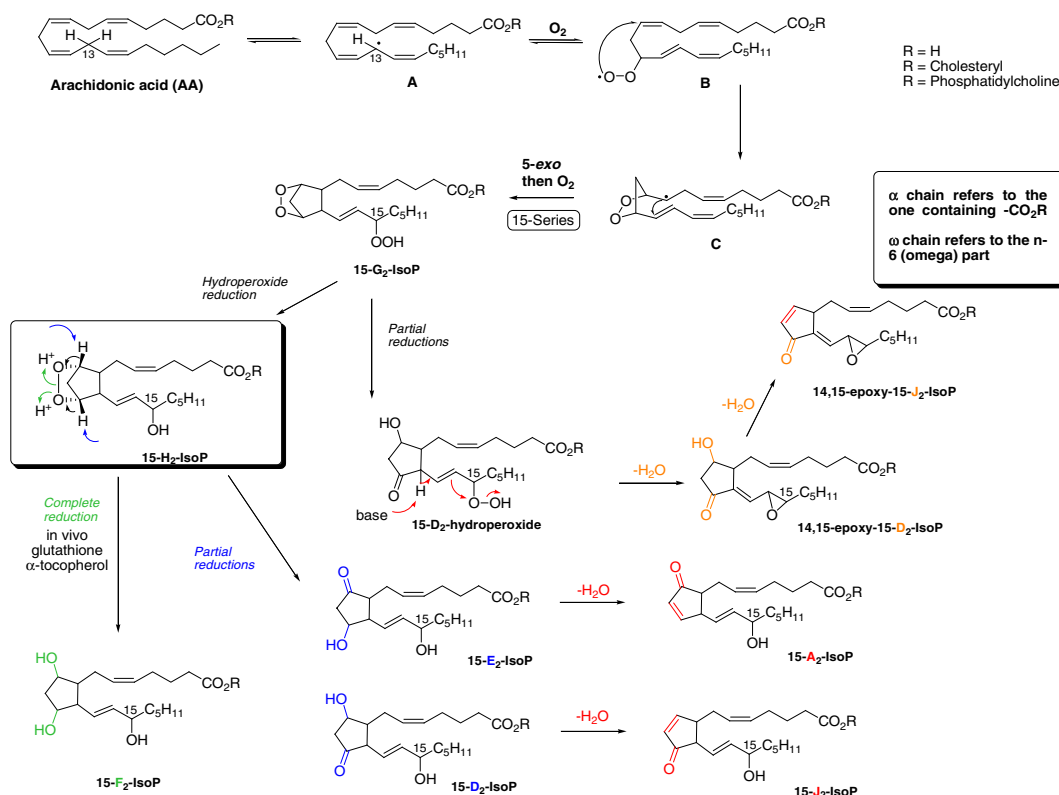
Unlike the IsoPs, the metabolism of neuroprostanes (NeuroPs) and phytoprostanes (PhytoPs) originating from docosahexaenoic acid (DHA) and α -linolenic acid (ALA) are not well elucidated. While the formation of NeuroPs and PhytoPs follows the same pathways as the IsoPs, their metabolism and excretion are yet poorly explored. Nevertheless, the importance of NeuroPs and PhytoPs as significant lipid mediators has clearly been established only in recent years [6–9].

In turn, understanding both, the chemistry and biology of the isoprostanoids (IsoPs, NeuroPs and PhytoPs) are necessary to improve the

Abbreviations: AA, Arachidonic acid; AD, Alzheimer's disease; AdA, Adrenic acid; ALA, α -Linolenic acid; APCI, Atmospheric pressure chemical ionization; BHT, Butylated hydroxytoluene; BSTFA, bis-(trimethylsilyl)trifluoroacetamide; CCl₄, Carbon tetrachloride; DHA, Docosahexaenoic acid; Dihomo-IsoP, Dihomo-isoprostane; DTPA, Diethylene tri-amine pentaacetic acid; ECNI, Electron-capture negative ionization; ELISA, Enzyme-linked immunosorbent assay; EPA, Eicosapentaenoic acid; ESI, Electrospray ionization; GC-MS, Gas chromatography mass spectrometry; GSH, Glutathione; IL, Interleukin; IsoP, Isoprostane; Keap1, Kelch-like ECH-associated protein 1; LC-MS, Liquid chromatography mass spectrometry; LPS, Lipopolysaccharides; MRM, Multiple-reaction monitoring; MS/MS, Tandem mass spectrometry; MTBE, Methyl tert-butyl ether; NeuroP, Neuroprostane; NF- κ B, Nuclear factor-kappaB; NPD1, Neuroprotectin D1; Nrf2, Nuclear factor erythroid 2-related factor 2; PDX, Protectin DX; PeCL, Poly- ϵ -caprolactone; PFBBBr, Pentafluorobenzyl bromide; PG, Prostaglandin; PhytoP, Phytoprostane; PPAR γ , Peroxisome proliferator-activated receptor gamma; PUFA, Polyunsaturated fatty acid; 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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Scheme 1. Biosynthesis of isoprostanoids type A, D, E, F and J and epoxy-isomers.

analytical approaches in order to understand the metabolism and biology of isoprostanoids. In this review, we present a concise overview of the current knowledge concerning the chemistry and biology of IsoPs, NeuroPs and PhytoPs and hope that our compendium will help others to further explore the biological relevance of isoprostanoids.

2. Understanding isoprostanoids *in vivo* formation

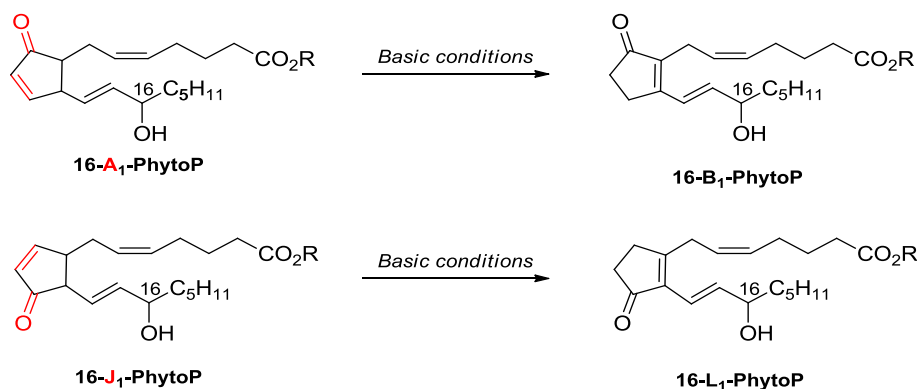
The word isoprostanoid refers to isomers of PGs. In fact, the lateral chains bearing by the cyclopentane ring are in 1,2-*trans* relationship (spatially opposed) for the PGs as they are in 1,2-*cis* relationship (in the same plane) for the isoprostanones (IsoPs). The biosynthesis of PGs is well established since the 1970s and involves enzymatic COX-mediated mechanisms. However, the formation of IsoPs was uncovered in the 1990s through publication in the field of PGs [1]. Morrow and co-workers showed that arachidonic acid (AA, C20:4 n-6) exposed to carbon tetrachloride (CCl_4) was oxidized *in vivo* to racemic IsoPs and racemic PGs, independent from any enzymatic COX action.

The biosynthesis of these metabolites, described in Scheme 1 is now well-established and proceeds through several radical steps [1,10]. Polyunsaturated fatty acids (PUFA) such as AA are composed of bis-allylic structures; double bonds separated by a methylene group ($-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-$), where α -hydrogen atoms are particularly easy to remove by the actions of free radicals, supported by the mesomeric stabilization of the resulting radical (Scheme 1). Physiologically, after oxidative stress injury and the release of free radicals in the cellular membranes, one hydrogen atom is abstracted from AA (intermediate A). The resulting carbon radical, in the presence of oxygen, further proceeds to form a peroxy radical (compound B) and eventually the formation of an endoperoxide carbon centred radical (compound C). This intermediate then proceeds through a cyclization step to form the cyclopentane ring. The second consecutive 5-*exo*-trig cyclization follows the radical chemistry rules (Baldwin rules [11,12]) and is the determinant step going along with the main PGs and IsoPs

difference (e. g. lateral chains relationships), as it predominantly leads to a *cis* configuration of the lateral chains along with the *trans* configuration (PG isomers). The generation of the cyclopentane ring results in the formation of another radical which reacts with molecular oxygen to produce an endoperoxide-hydroperoxide intermediate after final H-atom transfer, also known as G_2 -IsoP. Prior to the endoperoxide reduction, the hydroperoxide is first reduced to form the H_2 -IsoP.

Depending on the reductive conditions H_2 -IsoP may subsequently form several IsoP families. Once the endoperoxide is completely reduced (black and green arrows simultaneously in Scheme 1) it leads to the F-type of IsoPs; a cyclopentane ring with two alcohol functions (in green). If the endoperoxide is partially reduced (arrow in blue and black, one side of the ring only in Scheme 1), the types D- and E- of the IsoPs are produced where the cyclopentane bears a hydroxy-ketone (in blue). The D-type refers to the ketone ($-\text{C}=\text{O}$) moiety on the cyclopentane on the same side as the ω -chain. In the E-type the ketone moiety is on the same side as the α -chain. The ratio between F-type, and D- and E-types mainly depends on the number of reductive agents, e.g. glutathione and α -tocopherol, in cells [13]. Moreover, under physiological conditions, dehydration can occur especially in the hydroxyl-ketone structures (type D- and E-). Subsequently, A- and J-types (in red Scheme 1) of the IsoPs are formed by the dehydration of E- and D-type respectively. As like D- and E-types, A- and J-types are recognizable with the ketone moieties on the side of the α -chain (A-type) or ω -chain (J-type).

Other IsoP metabolites, such as the epoxy-isoprostanones (epoxy-IsoPs) are also formed *in vivo* and detected in mildly oxidized LDL of atherosclerotic lesions [14,15]. The epoxy-IsoPs biosynthesis (in orange Scheme 1) follows the same pathway as the formation of the G_2 -IsoP intermediate, but the endoperoxide is first reduced into the hydroperoxy- D_2 -IsoP compound. Then, dehydration occurs due to the acidity of the α -keto hydrogen atom and the hydroperoxy function, leading to the formation of an epoxide (orange arrows Scheme 1) to give epoxy- D_2 -IsoPs. Epoxy- D_2 -IsoPs were shown to dehydrate spontaneously to



Scheme 2. Generation of tetrasubstituted phytoprostanes (PhytoP) B₁ and L₁ in basic condition from cyclopentenone derivatives.

epoxy-J₂-IsoPs. Recently, epoxy-IsoPs were shown to exert anti-inflammatory activity and may be a valuable group of compounds in inflammatory diseases [15,16].

Two other types of isoprostanoids should also be noted; the B- and L-types (Scheme 2). Under basic conditions, A- and J-types undergo facile isomerization of the double bond. This isomerization is easily explained by the formation of the thermodynamically more stable metabolites. Therefore, the A-type isomerizes into B-type, the J-type leads to the L-type.

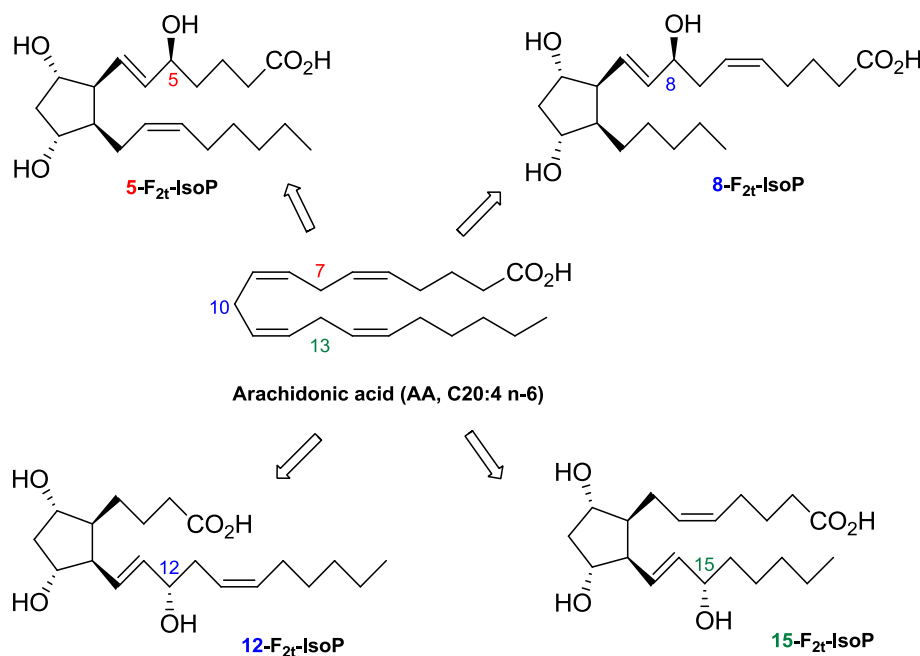
However, as AA and other PUFA have several *bis*-allylic positions in their structures allowing for numerous opportunities for free radical attack, not only the 15-series isoprostanoids as shown in Scheme 1 but also 5-, 8- and 12-series isomers can be produced. As described in Scheme 3, hydrogen abstraction on C7 (in red Scheme 3) will give the 5-series of IsoPs, whereas 8- and 12-series are produced through C10 hydrogen abstraction. Consequently, starting from AA, 4 series of IsoPs may be formed, 5-, 8-, 12- and 15-series, and it should be highlighted that the 5- and the 15-series are the most abundant [17,18]. Considering the unique formation of F-type IsoPs, the formation of 5 stereogenic centres give rise to 64 different IsoP isomers (enantiomers included).

Both n-6 and n-3 are essential PUFA in humans. The n-3 PUFA are frequently recommended because of possible health benefits. AA is the main n-6 PUFA in human cell membranes, whereas α -linolenic acid (ALA, C18:3 n-3) is the main n-3 PUFA in plant leaves. In fact, ALA

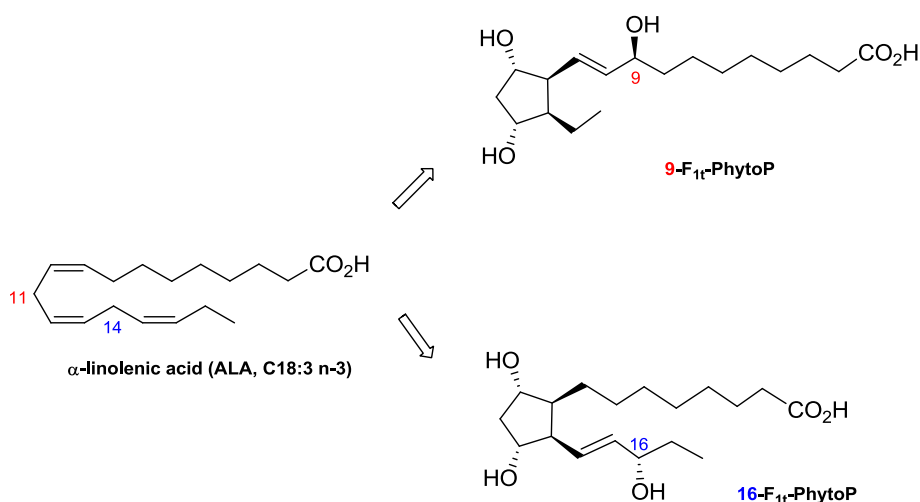
metabolites, were first discovered by Mueller and co-workers in 1998, and were named phytoprostanoids (PhytoPs) [19]. As shown in Scheme 4, ALA contains two *bis*-allylic positions (C11 and C14) leading to two series of F-type PhytoPs; the 9-series and the 16-series, namely 32 isomers (enantiomers included).

Eicosapentaenoic acid (EPA, C20:5 n-3) together with docosahexaenoic acid (DHA, C22:6 n-3) are mostly provided by the diet from marine resources such as fish or algae. The peroxidation of EPA [20] and its four *bis*-allylic positions will provide 6 series of IsoPs (5-, 8-, 11-, 12-, 15- and 18-, Scheme 5). The 5- and 18-series are highlighted to be the most abundant series among the other. As for DHA, 8 series can be formed (4-, 7-, 10-, 11-, 13-, 14-, 17- and 20-, Scheme 6). Predominant in the grey matter of the brain, the term neuro- was affixed and the DHA metabolites [21,22] were named NeuroPs. Among the metabolites, the 4- and 20-series were shown to be the most abundant [23].

Mostly found in the white matter of the brain, adrenic acid (AdA, C22:4 n-6) was probably the least considered PUFA, but due to its potential beneficial activities in humans AdA is now more and more studied. In order to differentiate AdA isoprostanoids from the AA derived ones, the term dihome-isoprostanoids (dihome-IsoPs) was introduced by VanRollins et al. in 2008 [24]. Four series of dihome-IsoPs are produced by AdA oxidation, namely the 7-, 10-, 14- and 17-series (Scheme 7), with the 7- and 17-series as the most abundant.



Scheme 3. The main F₃-isoprostanoid isomers derived from arachidonic acid. IsoP: isoprostanoid. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)



2.1. The use of organic synthesis to acquire isoprostanoid standards

The biosynthesis previously described, clearly demonstrates that isoprostanoids are found in biological systems as a complex mixture of isomers. In turn, this raises the question which isomer(s) is of physiological relevance or a possible biomarker? A single solution exists to efficiently answer the questions - by having the pure isomers at hand. Pure synthetic standards are often available from commercial sources, however even if the first IsoPs were discovered almost three decades ago, up to now, less than 10 pure isoprostanoid isomers are commercially available. Pure isoprostanoid sources are needed to better evaluate their role in lipid biology. Through total synthesis, research on isoprostanoids has been significantly advanced in the last decade [25,26].

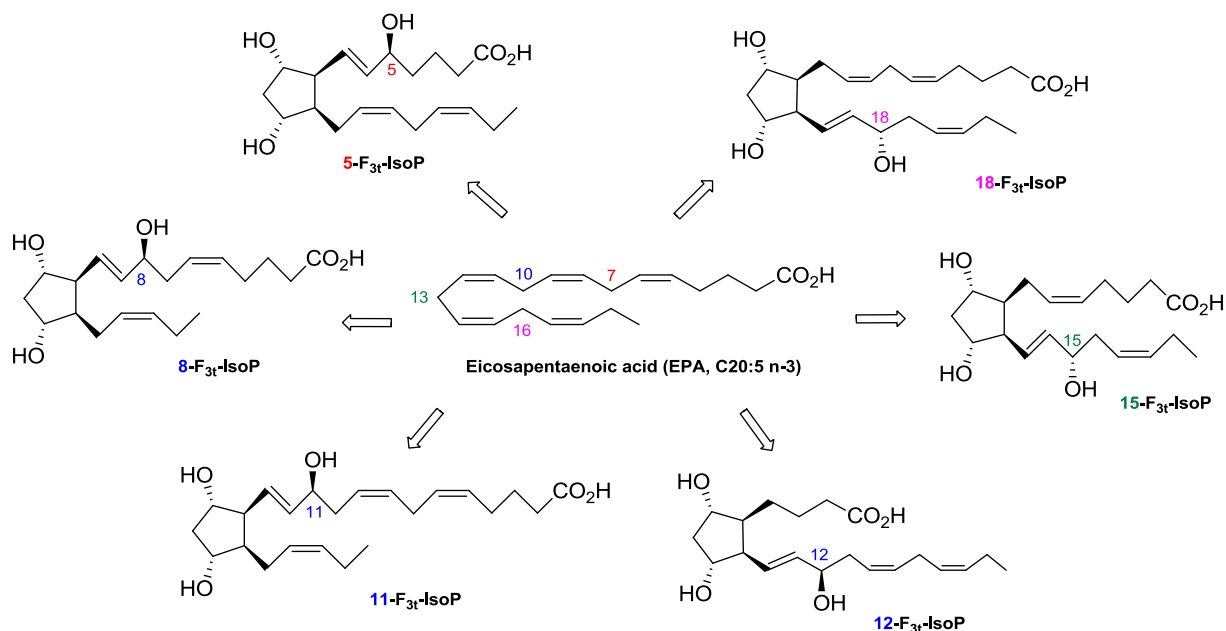
Throughout the years, the organic chemists' community developed several synthetic strategies that can be assembled together in three main concepts (Scheme 8). To clearly understand this chemistry part of this review, the structure of those isoprostanoids should be perceived. They are composed of one main cyclic core, which can possess different substituents, and to this core are attached two different lateral chains.

The first concept of the synthesis to be applied for these metabolites

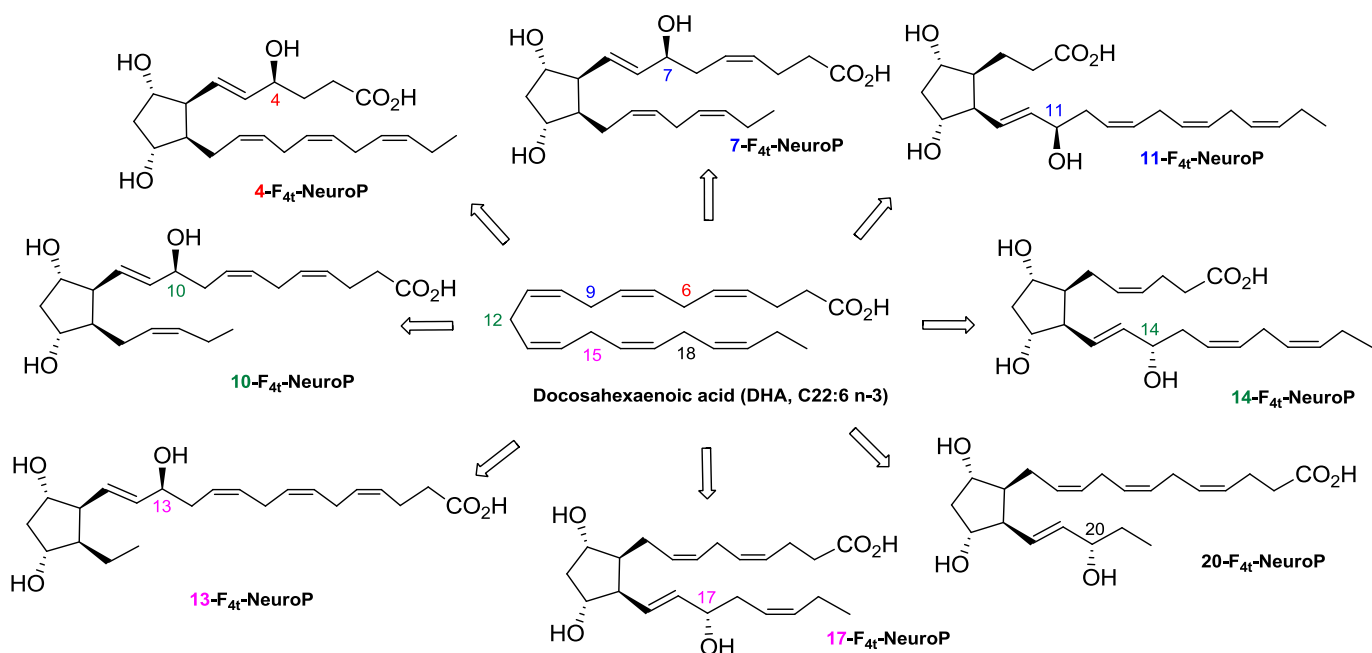
is to design the full structure of the molecule in a linear fashion and proceed to the formation of the core at the end of the synthesis (route no. 1, Scheme 8). The groups of Taber [27–35] and Durand/Rossi [36,37] used this strategy (Scheme 9). This approach has the advantage to mimic the biosynthesis and the chemist can expect that the late cyclization is accomplishable. However, toward the final intermediate the route is long, often difficult and at the end can be used for a limited variety of compounds.

Then, a second concept was developed. The idea is to realize the cyclization with one of the chains already present in the structure and add the second lateral chain thereafter (route no. 2, Scheme 8). Few groups used this strategy, such as Jahn [38,39] (Scheme 10) and Carreira [40], Weng/Lu [41] for the synthesis of epoxy-IsoPs. The biomimetic side is conserved while convergence and flexibility are brought on.

Finally, today's most preferred strategy is to synthesize the core and introduce the lateral chains one after the other (route nos. 2 and 3, Scheme 8). This strategy was largely applied by Larock/Lee [42], Rokach [43–46], Zanoni [47,48], Durand/Rossi [49–51], Vionnet/Renaud [52], Snapper [53–56] and Galano/Oger [57]. In the three examples shown in Scheme 11, different core structures are prepared before the



Scheme 5. F₃-isoprostanoid isomers derived from eicosapentaenoic acid. IsoP: isoprostanoid.



Scheme 6. Neuroprostane (NeuroP) isomers derived from docosahexaenoic acid.

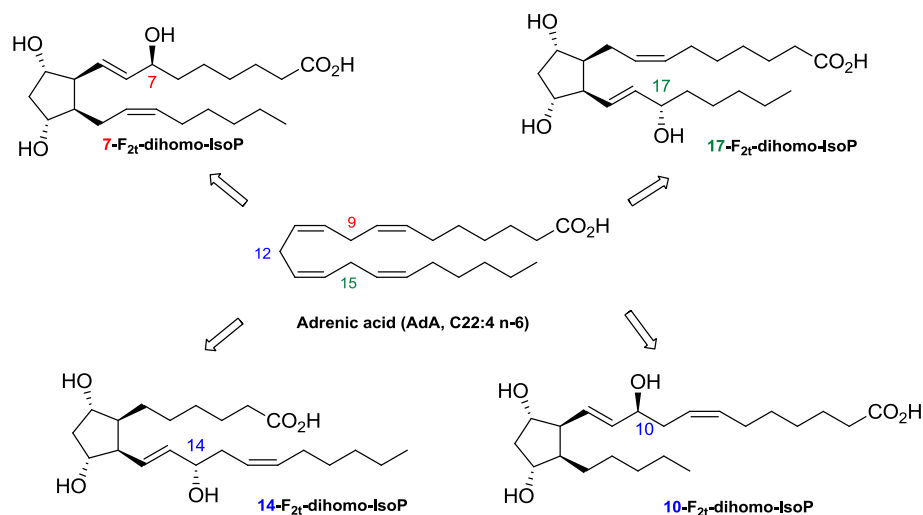
introduction of the first lateral chain, bicyclic (Zanoni, Snapper, Galano/Oger) or with the desired cyclopentane ring and two side groups (the side chains introduced in Galano/Oger Scheme) already in place. This approach is far from the biosynthetic route but has the major advantage to be flexible and will give access to a wide range of isoprostanoids i.e. different types (A, D, E, F and J), different stereochemistry's (*cis* or *trans* IsoPs) and allow starting from only one common intermediate. This strategy was also used for the synthesis of epoxy-IsoPs by the groups of Acharya/Kobayashi, Jung, Zhong [58–63].

To date, chemists are still developing syntheses of isoprostanoids to gain access to all the families together with their isomers and epimers. The research in the field of isoprostanoids is focused in their use as biomarkers and their biological activities.

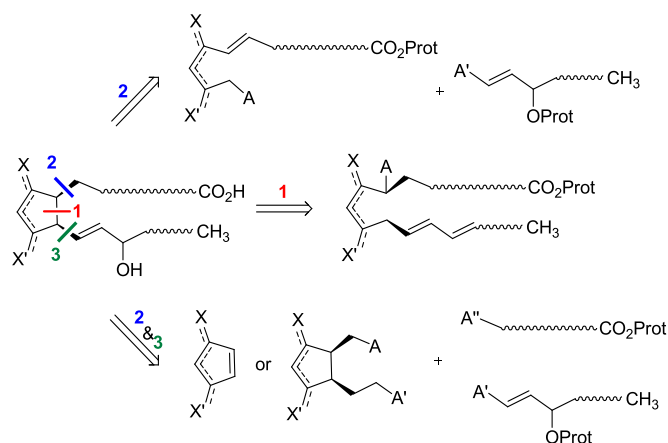
2.2. Metabolism

While the metabolism of the IsoPs, particularly 15-F_{2t}-IsoP has been described in detail [64], the metabolism of the NeuroPs and PhytoPs is much less studied. As shown in Fig 1, the main metabolic reactions are

β -oxidation and reduction, respectively. The NeuroPs, 4-F_{4t}-NeuroP and 10-F_{4t}-NeuroP have been investigated in human and animal studies related to neurological disorders [23,65], and interestingly, 4-F_{4t}-NeuroP was found mainly in the circulation and to a lesser extent in the urine whereas 10-F_{4t}-NeuroP were detectable in both body fluids (Fig 1). The metabolism of PhytoPs is even less well studied where only two reports were found in the literature. Karg's group identified that ingestion of plant oils by healthy males displayed slow absorption and excretion of PhytoPs and likewise, Barden et al. showed that ingestion of ALA (flaxseed oil) augmented F₁-PhytoP production in healthy human plasma but not in urine [8,11]. Although not yet experimentally proven, it is expected that the metabolism of NeuroPs and PhytoPs proceeds along the same pathways as observed for the IsoPs. As postulated in Fig 1 (dotted lines) β -oxidation and reduction would lead to 2,3,4,5-tetranor-10-F_{4t}-NeuroP and 2,3,4,5,6,7-hexanor-10-F_{4t}-NeuroP and 2,3,4,5,6,7-hexanor-16-F₁-PhytoP, three possible urinary metabolites. However, more work will be needed to map the metabolism and excretion routes of the NeuroPs and PhytoPs, helping to establish their use as possible new oxidative stress biomarkers.



Scheme 7. F₂-dihomo-isoprostane (dihomo-IsoP) isomers derived from adrenic acid.



Scheme 8. Retrosynthetic analysis of the three main synthetic strategies developed for isoprostanoids.

3. Isoprostanoid analysis

Morrow's group presented their study about, "one fresh plasma vs several months stored plasma" where they observed an increase in the formation of compounds that also occurred in other biological fluids [1,66]. This study marks the discovery of the racemic prostaglandin diastereoisomers which they later termed isoprostanones [67]. In recent years, a wide variety of non-enzymatic metabolites were identified, including AA, AdA, ALA, EPA, docosapentaenoic (DPA) and DHA derived autoxidation products [68,69]. From an analytical chemistry point of view, several characteristics make the analysis of isoprostanoids a challenging task. Firstly, to distinguish between enzymatic and non-enzymatic products, isomeric compounds including, diastereomers as well as geometric and positional isomers need to be distinguished [70]. Secondly, the usually low abundance of isoprostanoids demands high analytical sensitivity and thirdly, artefactual formation of isoprostanoids during sample treatment remains an important concern [71]. Several analytical procedures and techniques have arisen over the years; the most important ones will be discussed below.

3.1. Sample collection

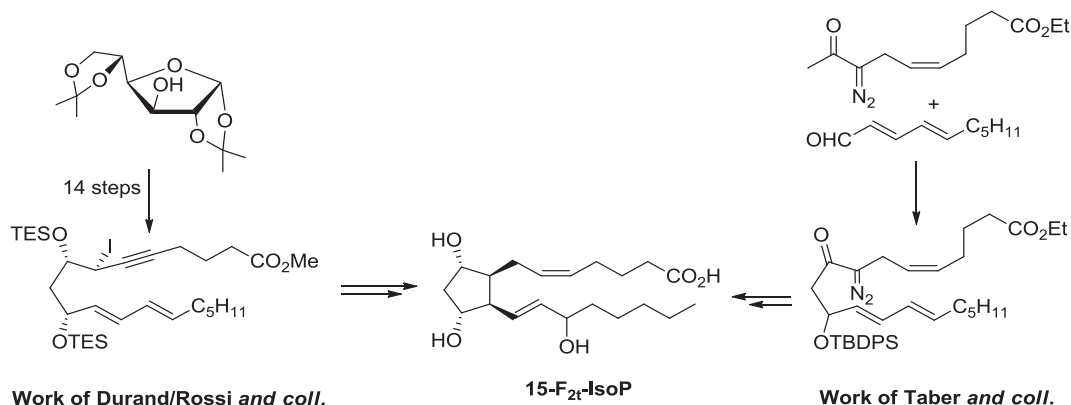
As mentioned before, due to the high reactivity of the *bis*-allylic hydrogen atoms, the double bonds found in PUFAs are prone to autoxidation and/or photodegradation, leading to generation of non-

enzymatic metabolites including isoprostanoids. In turn, artefactual isoprostanoid formation during bio-sampling, storage, extraction and derivatization is of great concern. It is therefore advised to take several precautions: i) during storage, oxygen should be eliminated from the samples by flushing the samples with nitrogen or argon, ii) a suitable antioxidant such as butylated hydroxytoluene (BHT), triphenylphosphine (TPP), diethylene tri-amine pentaacetic acid (DTPA) and glutathione (GSH) should be used, iii) in order to avoid the *ex vivo* enzymatic production of eicosanoids, a small amount of a cyclooxygenase inhibitor e.g. indomethacin is commonly added [72] and iv) most importantly all biological fluids and tissues must be kept at ultra-low temperature (i.e. $-80\text{ }^{\circ}\text{C}$) to ensure long term stability (6 months for plasma, several years for urine), ideally avoiding any freeze-thaw cycle. A detailed procedure for sample collection and storage has recently been described by Barden et al. [71].

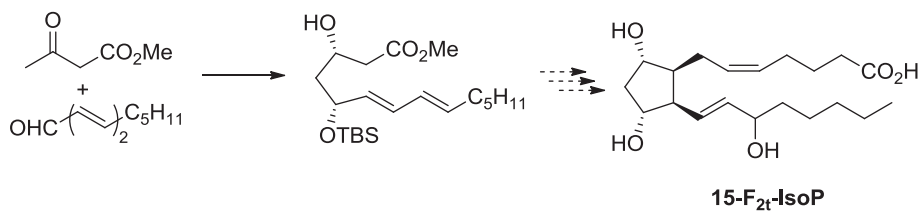
3.2. Sample preparation and extraction

Sample preparation vastly depends on the investigated matrix as well as the subsequently used analysis technique. In general, isoprostanoids can either be extracted from the matrix itself, or after a comprehensive lipid extraction step, following well established protocols such as Folch (chloroform/methanol, 2:1, v/v), Bligh and Dyer (chloroform/methanol, 1:2, v/v) or methyl *tert*-butyl ether (MTBE) extraction [73–75] are analyzed. For tissues, total (free and bound) isoprostanoids needs to be hydrolysed to release esterified isoprostanoids from the matrix [76]. Hydrolysis is usually performed by adding a methanolic or ethanolic alkaline solution to the sample, followed by gentle heating (e.g. 1 M KOH in methanol for 30 min at $37\text{ }^{\circ}\text{C}$) [77]. In the case of urinary samples, isoprostanoids are present in free form thus hydrolysis is not required, nevertheless some authors recommend pretreatment with glucuronidase to cleave glucuronide bound analytes and to reduce matrix effects [78].

The extraction of isoprostanoids from biological matrices usually involves solid phase extraction (SPE). Typical protocols include the use of reversed phase materials [79] and in case of urinary samples, weak-anion exchange materials [80]. The latter allows for dedicated washing procedures resulting in clean extracts, even from a highly challenging matrix including urine samples. Another popular extraction procedure, that has particularly been used in combination with gas chromatography mass spectrometry (GC-MS) is thin layer chromatography (TLC) [81]. Other less frequently applied techniques, include: combined SPE and TLC [82] as well as immunoaffinity based techniques, that can be useful for $15\text{-F}_{2t}\text{-IsoP}$ analysis, but not for omega-3 PUFA derived isoprostanoids, due to a lack of specific immobilized antibodies [83].



Scheme 9. Examples of biomimetic synthetic approaches.



Scheme 10. One chain containing structure prior to cyclization synthetic strategy.

3.3. Analysis

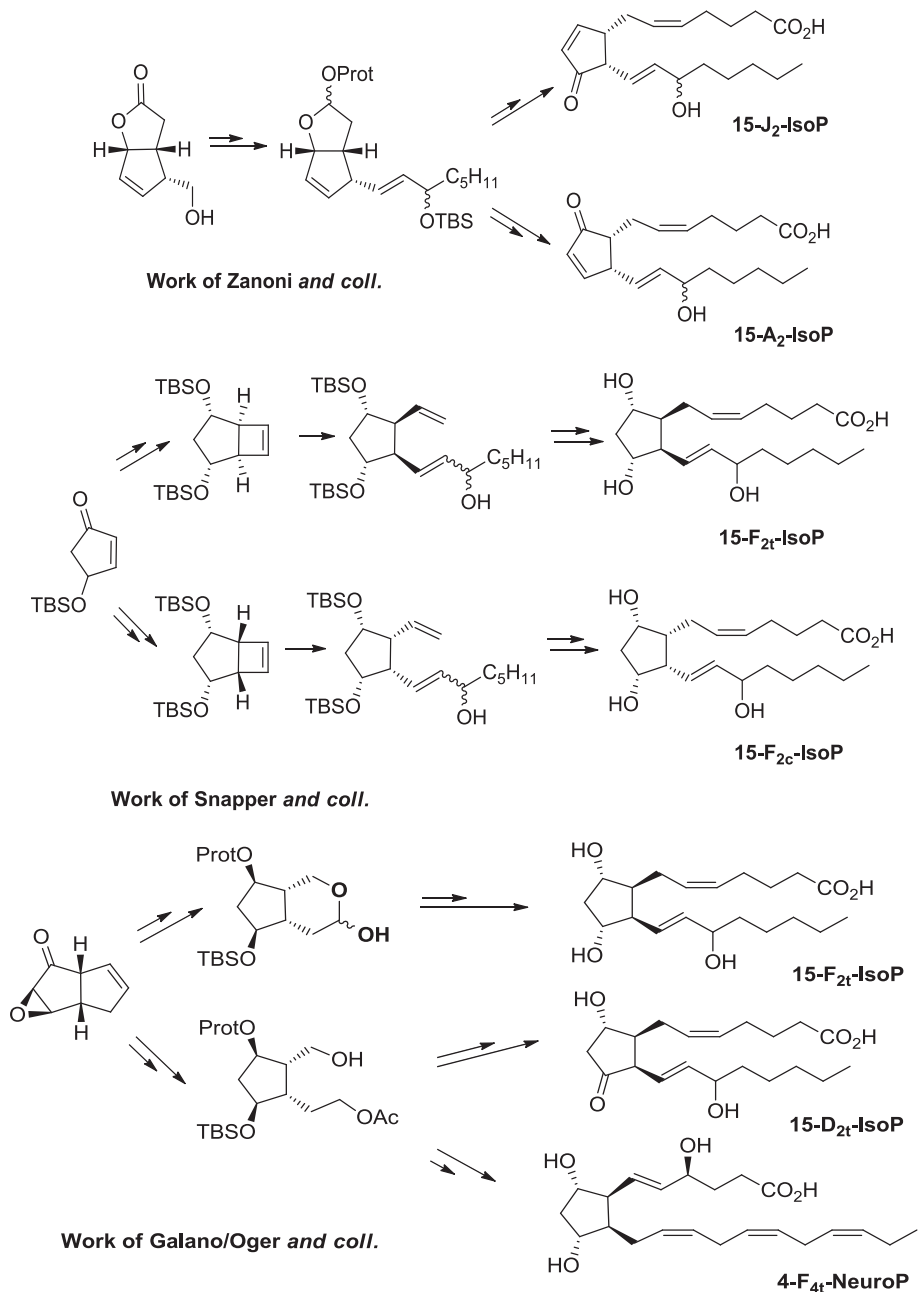
In principle, the analysis of isoprostanoids can be divided into immunological assays and mass spectrometry based techniques. However, enzyme linked immunosorbent assays (ELISA kits) and radioimmunoassays (RIA) are limited to a single component, 15-F_{2t}-IsoP and besides their intrinsic issue regarding specificity, it also presents severe limitations.

Mass spectrometry based analysis is usually carried out in combination with either gas or liquid chromatography (GC-MS, LC-MS) [81]. Both, GC-MS and LC-MS present specific advantages and disadvantages, which will briefly be discussed below. An excellent in-depth discussion has recently been described by Tsikas and Zoerner [84].

3.3.1. Derivatization

For GC-MS analysis, derivatization is mandatory. It is common to

Scheme 11. Examples of approaches for isoprostanoid without pre-introduction of the two chains.



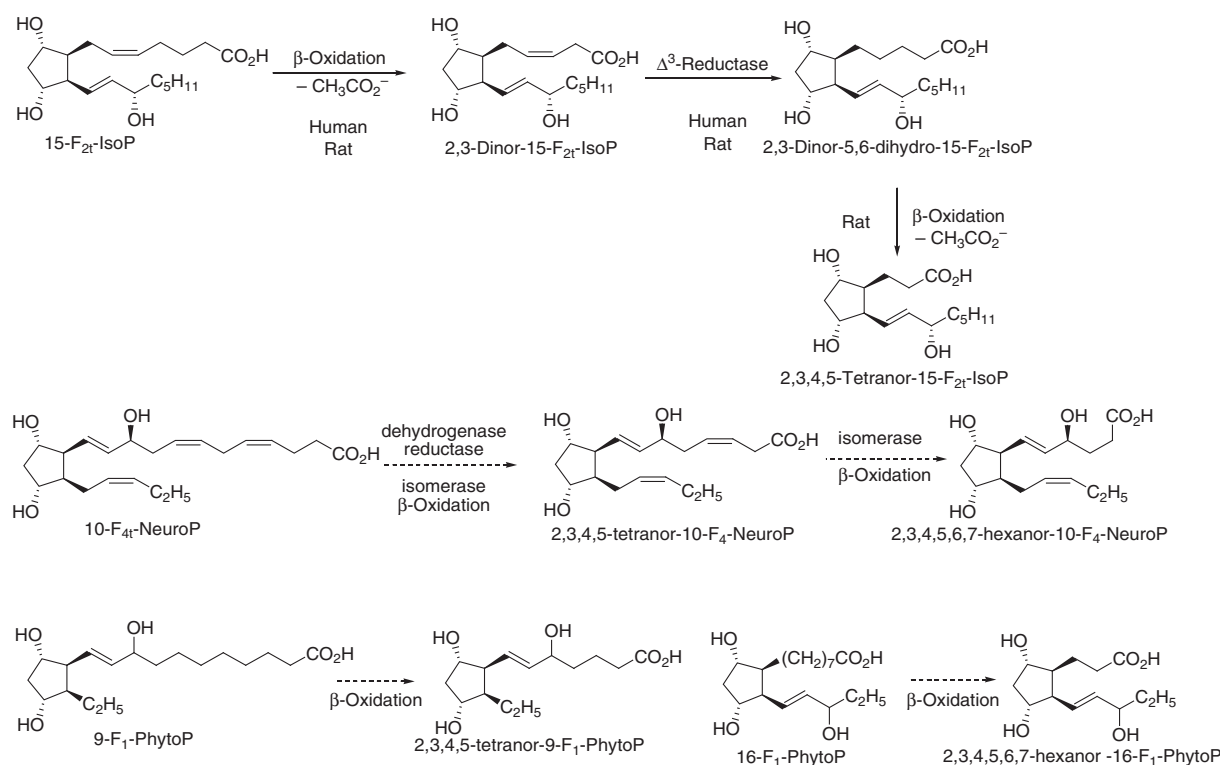


Fig. 1. Known metabolic pathways of 15-F_{2t}-IsoP, 10-F_{4t}-NeuroP, and 9-F₁-PhytoP and potential metabolites for excretion. IsoP: isoprostane; NeuroP: neuroprostane; PhytoP: phyto-prostane.

initially convert carboxylic acid function into pentafluorobenzyl esters (PFB) by reacting the samples with pentafluorobenzyl bromide (PFBBR) using a base catalyst such as *N,N'*-diisopropylethylamine. Subsequently, hydroxyl functions are silylated with either *bis*-(trimethylsilyl)trifluoroacetamide (BSTFA) or *N*-methyl-*N*-trimethylsilyltrifluoroacetamide with or without the use of a catalyst [70,85]. Although derivatization is not mandatory for LC based isoprostanoïd analysis, some groups addressed the possibility of facilitating electro-spray ionization in positive mode (ESI+) using dedicated derivatization strategies as well as using bromine labelled reagents for isotope pattern recognition [86,87]. However, to date, no study could clearly prove the benefits of isoprostanoïd derivatization prior LC-MS analysis [88]. 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 over the years increased mass spectrometer sensitivity in negative mode ESI (ESI-), allowing the analysis of native isoprostanoïds.

3.3.2. GC-MS and GC-MS/MS analysis

Traditionally, isoprostanoïds have been analyzed using GC-MS [81]. Even though the GC based analysis requires sample derivatization, the resolving power of the GC is unprecedented. Mainly due to a virtually absent eddy diffusion, GC analysis achieves very high plate numbers and in turn, is ideally suited for the analysis of closely related substances, such as the isoprostanoïds. With respect to MS detection, over the years several ionization techniques have been tested, however, electron-capture negative ionization (ECNI) using methane as the reagent gas, has become the gold standard. Especially in combination with PFB esters, ECNI allows the generation of molecular ions, which are usually monitored either in selected-ion monitoring (SIM) or multiple-reaction monitoring (MRM) mode, when using tandem mass spectrometry (GC-MS/MS). Particularly, the latter allows gaining selectivity by choosing analyte specific fragments [89]. Advanced protocols for GC-MS and GC-MS/MS analysis have recently been published by Tsikas et al. [90].

3.3.3. LC-MS and LC-MS/MS analysis

Due to the isoprostanoïd low abundance and the high selectivity needed for proper isoprostanoïd analysis, LC is usually coupled to tandem mass spectrometer (LC-MS/MS), making use of MRM on triple-quadrupole or quadrupole linear ion trap (QTrap) type instruments. With respect to the commonly applied ionization techniques, some authors have described the use of atmospheric pressure chemical ionization in the negative mode (APCI-) [91]. However, by far, the most frequently applied technique is ESI-.

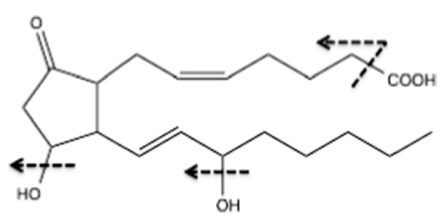
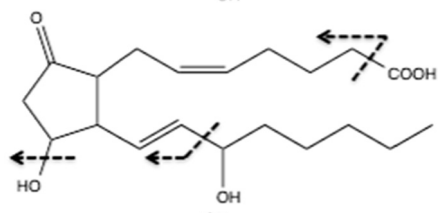
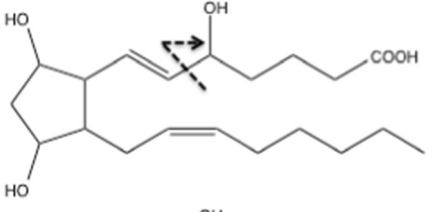
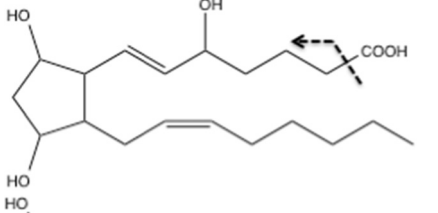
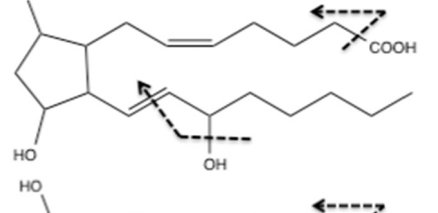
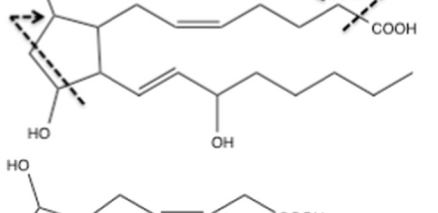
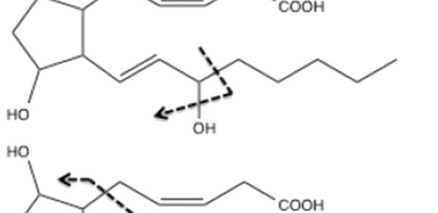
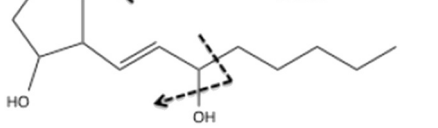
LC-MS/MS has the advantage to select analyte characteristic fragment ions, for example related to the position of hydroxyl function within the molecule [92]. A complete set of fragmentation and ion transitions from the precursors of the known isoprostanes are compiled in Table 1. While carefully chosen MRM transitions allow to readily classify isoprostanes belonging to the 5, 8, 12 or 15-series, the identification of geometric isomers as well as enantiomers, demands chromatographic separation as well as the availability of synthetic standards. An example for the characteristic fragmentation of positional NeuroP isomers are 4-F_{4t}-NeuroP and 10-F_{4t}-NeuroP which can be distinguished based on the MRM transitions m/z 377- > 101 for 4-F_{4t}-NeuroP and m/z 377- > 153 for 10-F_{4t}-NeuroP [93] (Table 1).

An upcoming technique which in the future might facilitate the separation of isomers, closely eluting in the LC is ion-mobility-spectrometry [94]. However, to the best of our knowledge applications in the field of isoprostanoïd analysis remain very limited [95]. It should be noted that not all the isoprostanoïds have been evaluated in biological specimen and analyses of PhytoPs are mainly conducted in food and plant samples whereas those of IsoPs and NeuroPs are mainly assessed in mammalian tissues and fluid. What is lacking is the evaluation of PhytoPs in mammalian tissues since ALA is an essential PUFA required in mammals. Furthermore, it should be highlighted that not all mammalian specimen may contain all the isoprostanoïds [96,97] and this may depend on the metabolism and the experimental model evaluated [79].

As reference material, a list of the most abundant MS/MS transitions

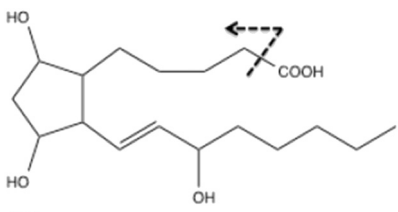
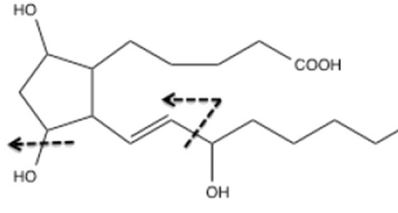
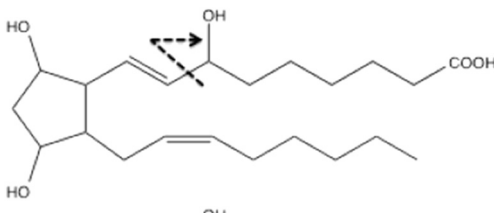
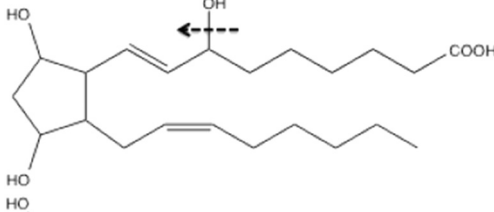
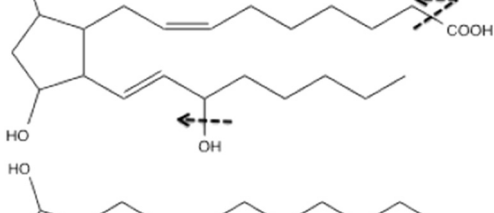
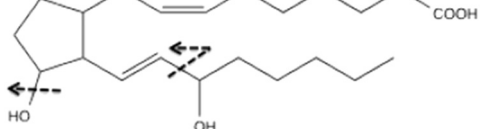
Table 1

Isoprostanoid characteristic fragmentations and sample materials with described appearance. For additional analytical characteristics please refer to Supplementary information (List 1).

Compounds	Precursor/ product ion <i>m/z</i>	Presumed fragmentation	Sample	Reference
Arachidonic acid 15(<i>RS</i>)-15- <i>E</i> ₂₁ -IsoP	T1: 351.2/ 271.0		Mouse brain	[92]
	T2: 351.2/ 189.1			
5(<i>RS</i>)-5- <i>F</i> ₂₁ -IsoP	T1: 353.2/ 115.0		Human plasma Human brain Human CSF Mouse plasma Mouse liver Mouse brain Pig brain Mouse muscle Rat kidney Rat liver	[157,158] [159] [159] [157] [157] [157] [160] [157] [161] [161]
	T2: 353.2/ 309.0			
15(<i>RS</i>)-15- <i>F</i> ₂₁ -IsoP	T1: 353.2/ 193.0		Human plasma Human urine Human CSF Human exhaled breath condensate Human amniotic fluid Human brain Mouse plasma Mouse liver Mouse brain Pig brain Rat kidney Rat liver Fish muscle	[157,158,162,163] [162,164-166] [159] [167,168] [169] [159] [157] [157] [157] [160] [161] [161] [170]
	T2: 353.2/ 247.0			
2,3-dinor-15- <i>epi</i> -15- <i>F</i> ₂₁ -IsoP	T1: 325.2/ 237.1		Human urine Fish muscle tissue	[164,166] [170]
	T2: 325.2/ 137.0			

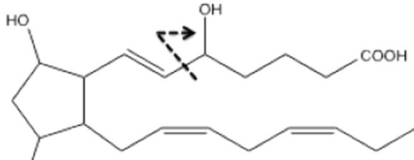
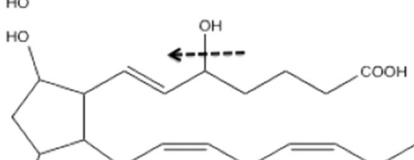
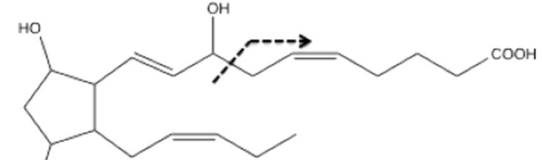
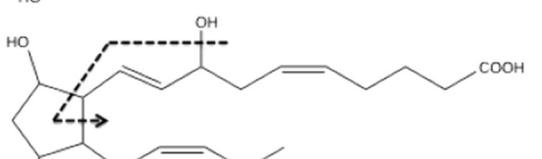
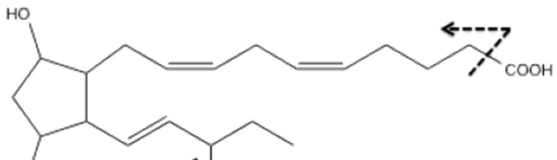
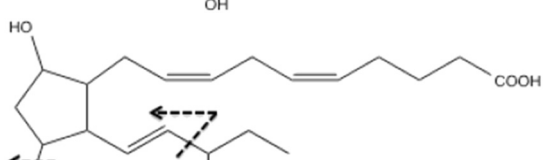
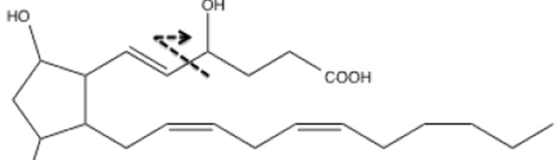
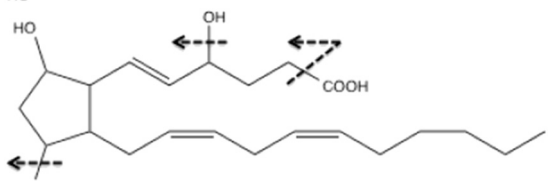
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Table 1 (continued)

Compounds	Precursor/ product ion <i>m/z</i>	Presumed fragmentation	Sample	Reference
<i>ent</i> -2,3-dinor-5,6-dihydro-15-F ₂₁ -IsoP	T1: 327.2/ 283.2		Human urine Fish muscle tissue Mouse urine	[164] [170] [157]
	T2: 327.2/ 209.1			
Adrenic acid 7(<i>RS</i>)-7-F ₂₁ -dihomo-IsoP	T1: 381.3/ 143.0		Human urine Pig brain	[171] [160]
	T2: 381.3/ 363.1			
17(<i>RS</i>)-17-F ₂₁ -dihomo-IsoP	T1: 381.3/ 319.2		Human urine Pig brain tissue Mouse brain	[171] [160] [157]
	T2: 381.3/ 263.1			

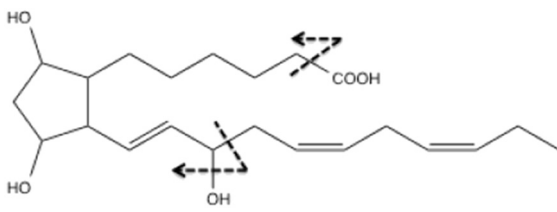
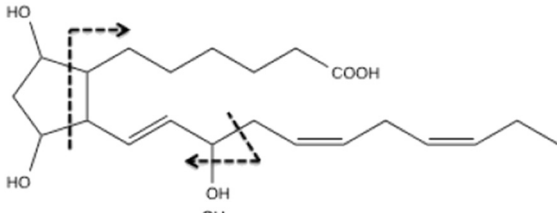
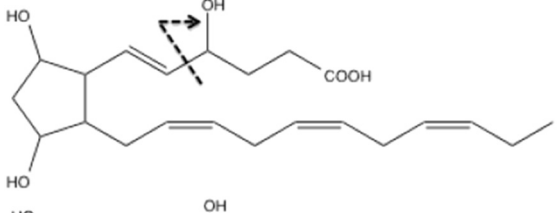
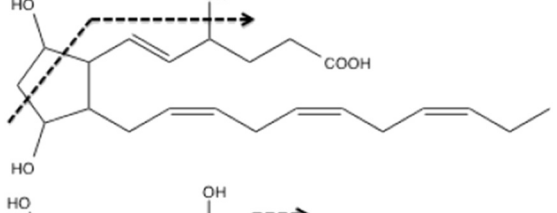
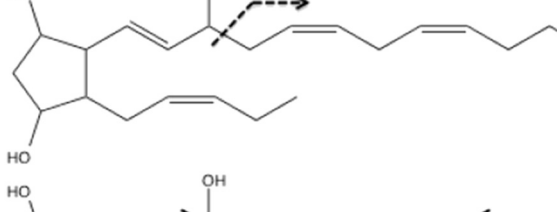
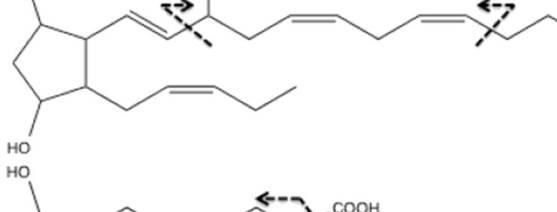
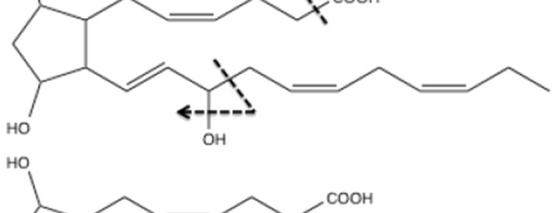
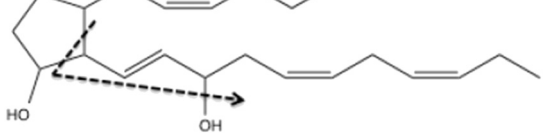
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Table 1 (continued)

Compounds	Precursor/ product ion <i>m/z</i>	Presumed fragmentation	Sample	Reference
Eicosapentaenoic acid 5(<i>RS</i>)-5- F_{3r} -IsoP	T1: 351.2/ 115.0		Nematode Fish muscle	[172] [170]
	T2: 351.2/ 333.0			
8(<i>RS</i>)-8- F_{3r} -IsoP	T1: 351.3/ 127.1			
	T2: 351.3/ 155.0			
18(<i>RS</i>)-18- F_{3r} -IsoP	T1: 351.2/ 289.1			
	T2: 351.2/ 275.0			
Docosahexaenoic acid 4- F_{3r} -NeuroP	T1: 379.2/ 101.0		Human urine	[171]
	T2: 379.2/ 299.3			

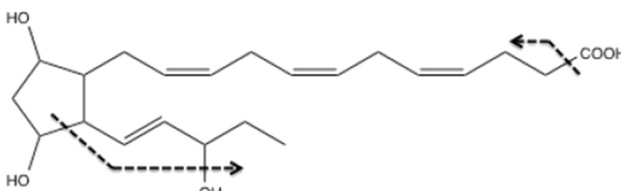
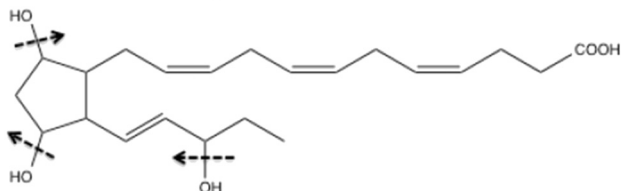
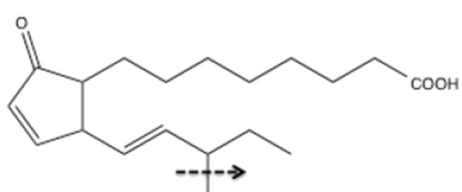
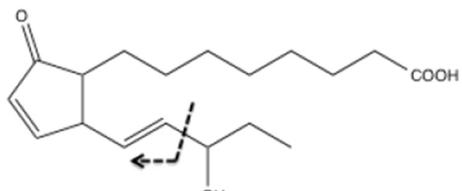
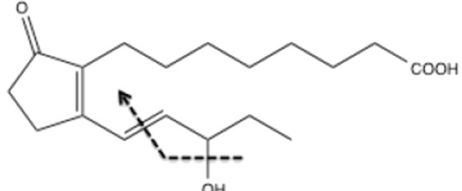
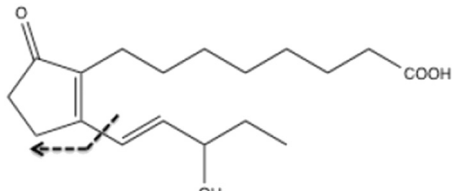
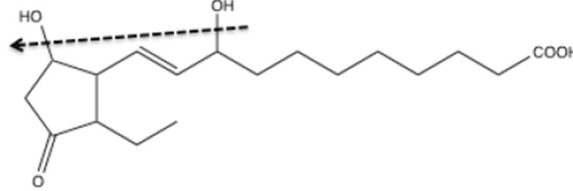
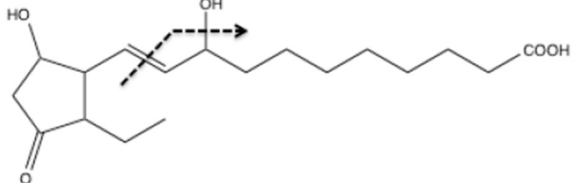
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Table 1 (continued)

Compounds	Precursor/ product ion <i>m/z</i>	Presumed fragmentation	Sample	Reference
14-F _{3t} -NeuroP	T1: 379.3/ 207.0			
	T2: 379.3/ 179.0			
4(RS)-4-F _{4t} -NeuroP	T1: 377.2/ 101.0		Human urine Pig brain tissue Human plasma Mouse liver Mouse brain	[171] [160] [157] [157] [157]
	T2: 377.2/ 271.3			
10(RS)-10-F _{4t} - NeuroP	T1: 377.2/ 153.0		Human urine Pig brain tissue Human plasma Mouse liver Mouse brain	[171] [160] [157] [157] [157]
	T2: 377.2/ 110.1			
14(RS)-14-F _{4t} - NeuroP	T1: 377.2/ 205.0			
	T2: 377.2/ 161.0			

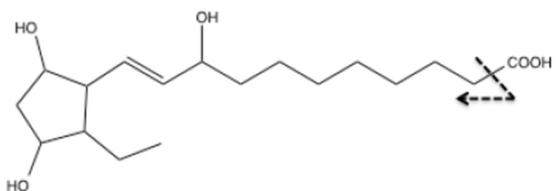
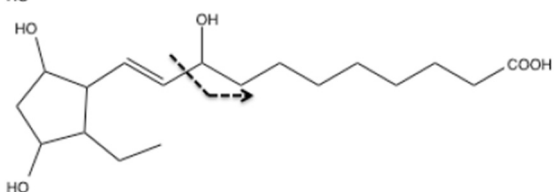
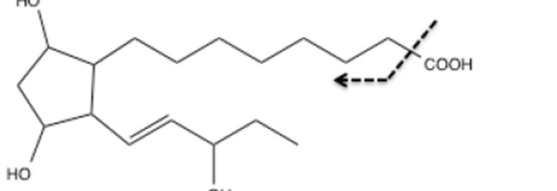
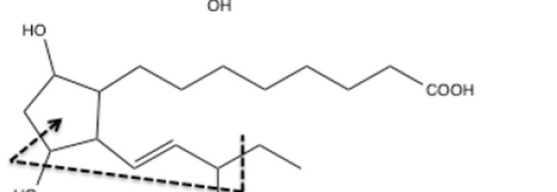
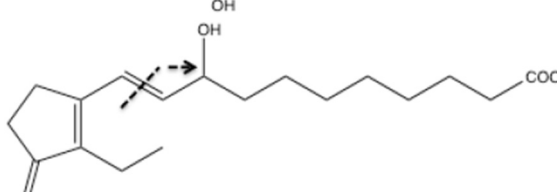
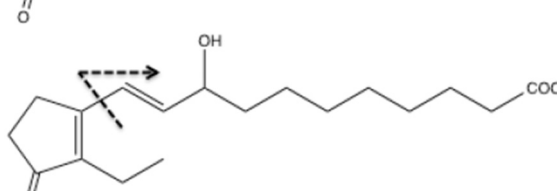
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Table 1 (continued)

Compounds	Precursor/ product ion m/z	Presumed fragmentation	Sample	Reference
20(RS)-20-F ₄₁ - NeuroP	T1: 377.3/ 315.2			
	T2: 377.3/ 323.0			
α -Linolenic acid 16(RS)-16-A ₁₁ - PhytoP	T1: 307.2/ 289.2		Plant cell culture: <i>N. tabacum</i> , <i>G. max</i> , <i>R. serpentina</i> , <i>A. tenuis</i>	[19]
	T2: 307.2/ 249.0			
16-B ₁₁ -PhytoP	T1: 307.2/ 235.0		Walnut, Macadamia, Pecan Almonds Olive oil, Sunflower oil <i>Passiflora edulis</i> Sims. Shell Macroalgae Melon leaves	[173] [113] [174] [175] [176] [177]
	T2: 307.2/ 223.0			
9(RS)-9-D ₁₁ -PhytoP	T1: 325.0/ 289.0		Walnut, Macadamia, Pecan Almonds Olive oil, Sunflower oil <i>Passiflora edulis</i> Sims. Shell Macroalgae Melon leaves	[173] [113] [174] [175] [176] [177]
	T2: 325.0/ 123.0			

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Table 1 (continued)

Compounds	Precursor/ product ion m/z	Presumed fragmentation	Sample	Reference
9(RS)-9-F ₁₁ -PhytoP	T1: 327.2/ 283.2		Walnut, Macadamia, Pecan Almonds Olive oil, Sunflower oil <i>Passiflora edulis</i> Sims. Shell Macroalgae Melon leaves	[173] [113] [174] [175] [176] [177]
	T2: 327.2/ 171.2			
ent-16(RS)-16-F ₁₁ -PhytoP	T1: 327.2/ 283.2		Walnut, Macadamia, Pecan Almonds Olive oil, Sunflower oil <i>Passiflora edulis</i> Sims. Shell Macroalgae Melon leaves	[173] [113] [174] [175] [176] [177]
	T2: 327.2/ 251.2			
9-L ₁₁ -PhytoP	T1: 307.2/ 185.1		Walnut, Macadamia, Pecan Almonds Olive oil, Sunflower oil <i>Passiflora edulis</i> Sims. Shell Macroalgae Melon leaves	[173] [113] [174] [175] [176] [177]
	T1: 307.2/ 197.0			

Arrow in the compound structure indicates the cleavage of the product ion from the precursor. T1: transition 1; T2: transition 2; IsoP: isoprostane; dihome-IsoP: dihome-isoprostane; NeuroP: neuroprostane; PhytoP: phytoprostane.

for a series of isoprostanoids is provided in Table 1. In addition, an analytical database containing analytical settings and tandem mass spectra of over 20 isoprostanoids can be found in the Supplementary Information (List 1).

4. Biomarkers in biological systems

Since the discovery of IsoPs, 15-F_{2t}-IsoP has been labelled as the biomarker for oxidative stress in human diseases. Notably, isoprostanoid measurements have been performed in mammalian plasma, urine, cerebrospinal fluid, sputum, saliva, exhaled breath condensate, brain tissues, atherosclerotic plaques and even gastric mucosa. More recently, the use of IsoPs as biomarkers has been extended to the marine ecosystem and includes environmental studies, and should be

recognized that one large part of PUFA in the human diet is obtained through our marine resources, e.g. seafood and algae. Notwithstanding, plant oil is also an important source of PUFA for the human body. Studies on the use of PhytoPs from ALA as biomarkers to evaluate plant oil oxidation from seeds, nuts, leaves, olives and wine have been reported recently. The quality of both marine and plant oils is important for general health and well-being as they are the source of essential fatty acids in our diet; without doubt, increase in oxidative stress biomarkers are good indicators for the PUFA quality. Although NeuroPs were utilized to measure oxidative stress related to diseases, this has not been fully utilized for measurement in the marine ecosystem. Yet, the extent of use as biomarkers in human studies is not large for NeuroPs compared to IsoPs, but has shown to be an important indicator in studies of oxidative stress related to neurodegeneration and neurological

conditions. In this part, we will explore reports on the use of isoprostanoid biomarkers and their applications in different biological areas. Not all studies on human diseases and IsoP biomarkers are included, as to date (2017), > 2500 articles related to isoprostanes are found in PubMed. Only those reports on prospective studies will be highlighted.

4.1. Isoprostanes

4.1.1. Human diseases

Lipid peroxidation is a critical component of oxidative stress, which is a common biological condition in a wide range of diseases such as, but not limited to, neurological disorders, cardiovascular diseases, diabetes and renal dysfunction [69]. Since its discovery, levels of F₂-IsoPs, especially 5-F_{2t}-IsoP and 15-F_{2t}-isoP, and their metabolites are routinely measured in non-invasive patient samples, predominantly in blood plasma and urine. Arachidonic acid is esterified in membranes and it is a ubiquitous component of mammalian cell membranes. Elevation of F₂-IsoPs *in vivo* represents the presence of cellular oxidant injury. The detection and quantification of F₂-IsoPs and its metabolites has been described in Section 3.

So far, ECNI-GC-MS remains the gold standard for F₂-IsoPs measurement due to its superior selectivity and sensitivity. Table 2 reviews the use of 5- and 15-series F₂-IsoPs and 15-F_{2t}-IsoP metabolites as biomarkers in several human diseases relating to oxidative stress. Although *in vitro* studies and in animal models using F₂-IsoPs has remarkably shown to be a reliable oxidant injury biomarker, the same does not hold true for all oxidative stress related diseases in humans that was illustrated by van't Erve et al. [98]. After meta-analysis of studies in different disease conditions, the authors pointed out that 'total' 15-F_{2t}-IsoP should be considered before interpreting non-enzymatic oxidative damage as generation of 'free' 15-F_{2t}-IsoP can be induced by inflammation-induced prostaglandin endoperoxide synthase [98]; further studies are needed to justify this finding. Similarly, it is worth mentioning that the experimental results in Table 2 indicate, regardless of the samples used, conflicting data is noted and failed to prove that either F₂-IsoPs or 15-F_{2t}-IsoP metabolites are suitable biomarkers for widespread diseases, such as Alzheimer's disease and type 2 diabetes. While few reports on less prevalent diseases like dengue fever [99] and periodontal disease [100] were distinguished, F₂-IsoPs appear to be significant biomarkers of these diseases. Thus, F₂-IsoPs or their metabolites might not be suitable biomarkers for all human diseases related to oxidative stress. Nonetheless, it is worth noting that the elevation of 15-F_{2t}-IsoP in cardiovascular diseases is more consistent than those in neurological disorders, and it is not surprising as 15-F_{2t}-IsoP is a vasoconstrictor. So far, although F₂-IsoPs are widely recognised as the biomarker for oxidative stress, no large-scale population study has been conducted using the MS platforms and, therefore, warrants a need to validate if it is a good biomarker for all oxidative stress related diseases, including neurodegenerative diseases.

In contrast to F₂-IsoPs, AdA-derived F₂-dihomo-IsoPs have shown to be potential biomarkers for brain white matter related conditions, where AdA is highly abundant. Studies in patients with neurological disorders, such as Rett Syndrome [101] showed significant elevation of plasma F₂-dihomo-IsoPs, and urinary 7-F_{2t}-dihomo-IsoPs. 17-F_{2t}-dihomo-IsoPs were shown to be higher in epileptic patients compared to controls [102]. In a recent report, F₂-dihomo-IsoPs were used as biomarker of the neuromotor system in adult triathletes. The study showed that physical exercise exerted different responses in the type of F₂-dihomo-IsoPs; urinary 17-F_{2t}-dihomo-IsoPs were elevated and 7-F_{2t}-dihomo-IsoPs decreased with increment of training load [103].

4.1.2. Marine ecosystem and environmental stressors

The use of F₂-IsoPs as biomarker for *in vivo* oxidant injury is not only limited to human diseases, but were also found in marine fishes as well as humans and animals that were exposed to environmental stressors

Table 2
15-F_{2t}-IsoPs and metabolites (15-F_{2t}-IsoP-M) and 5-F_{2t}-IsoPs (+) used as biomarkers to indicate human disease status related to oxidative stress published up to 2016.

Subjects	Sample	Disease vs control	Method	Reference	
Neurological Alzheimer's disease	Brain tissue (19)	↑	GC-MS	[178]	
	Urine (9)	↔	GC-MS	[179]	
	Plasma				
	Free (12)	↔			
	Total (12)	↔			
	CSF (41)	↑	GC-MS	[180]	
	Urine (56)				
	15-F _{2t} -IsoP	↔			
	15-F _{2t} -IsoP-M	↔			
	Urine ⁺ (50)	↑	GC-MS	[181]	
	Plasma ⁺ (50)	↑			
	CSF ⁺ (50)	↑			
	Brain tissue (5)	↔	GC-MS	[182]	
	Plasma (49)	↔	GC-MS	[183]	
	CSF (9)	↔	GC-MS	[184]	
Parkinson's disease	Brain tissue (6)	↔	GC-MS	[185]	
	Brain tissue (7)	↔	GC-MS	[182]	
	Plasma (47)	↔	GC-MS	[183]	
	Plasma (25)	↔	GC-MS	[99]	
	Anterior cingulate cortex (9)	↑	GC-MS	[186]	
	Occipital cortex (9)	↔			
	Brain tissue (10)	↔	GC-MS	[185]	
Schizophrenic	Plasma (134)	↑	GC-MS	[187]	
	Urine (11)	↔	GC-MS	[179]	
Huntington's disease	Plasma				
	Free (20)	↔			
	Total (19)	↔			
Mild cognitive impairment	Urine ⁺ (33)	↑	GC-MS	[181]	
	Plasma ⁺ (33)	↑			
	CSF ⁺ (33)	↑			
	Plasma (47)	↔	GC-MS	[183]	
Multiple system atrophy	CSF (9)	↔	GC-MS	[184]	
	Brain tissue (4)	↔	GC-MS	[182]	
	Dementia				
Stroke	Brain tissue (4)	↔	GC-MS	[182]	
	Plasma (21)		GC-MS	[99]	
Brain injury Aneurysmal subarachnoid hemorrhage (aSAH)	Total	↑			
	Free	↔			
	Urine	↑			
	Plasma (44)	↑	GC-MS	[188]	
	Urine (82)	↑	ELISA	[189]	
	CSF (18)	↑	GC-MS	[190]	
	Traumatic brain injury (TBI)	CSF (18)	↔	GC-MS	[191]
		Plasma (15)	↑		
	Epilepsy	CSF (15)	↑		
		Urine (60)	↑	ELISA	[192]
Down syndrome	Plasma (34)	↑	GC-MS	[193]	
	Urine (48)		LC-MS/MS	[194]	
Reversible cerebral vasoconstriction syndrome	15-F _{2t} -IsoP-M	↔			
	Urine (103)	↑	LC-MS/MS	[195]	
Autism (children)	Plasma (29)	↑	GC-MS	[196]	
	Plasma (44)	↑	ELISA	[197]	
Intermittent explosive disorder	Plasma (69)	↑	ELISA	[198]	
Hypoxic-ischemic encephalopathy	Cord serum (20)	↑	LC-MS/MS	[199]	
Neuroborreliosis	Plasma (22)		LC-MS/MS	[200]	
	Total	↑			
	Free	↑			
	Urine (22)	↑			
	CSF (22)	↑			

(continued on next page)

Table 2 (continued)

Subjects	Sample	Disease vs control	Method	Reference
Cardiovascular				
Asymptomatic and symptomatic atherosclerosis	Carotid plaques (30)	↑	LC-MS/MS	[201]
Mild-Moderate hypertension	Urine (30)	↔	GC-MS	[202]
Hypertension	Plasma (155)	↔	GC-MS	[203]
	Urine (155)	↔		
	Urine (31)	↑	ELISA	[204]
	Plasma (22)	↑	ELISA	[205]
	Urine (22)	↑		
	Urine (116)	↔	ELISA	[206]
Obstructive sleep apnea	Plasma (128)	↑	ELISA	[207]
	Urine (86)	↑	LC-MS/MS	[208]
Coronary artery disease	Urine (799)	↑	ELISA	[209]
Peripheral artery disease	Plasma (115)	↑	ELISA	[210]
Heart failure	Plasma (36)	↔	GC-MS	[211]
Cancer				
Prostate	Urine (304)	↑	ELISA	[212]
Uterine leiomyomas (fibroids)	Urine (20)	↔	ELISA	[213]
Breast	Urine (79)	↔	RIA	[214]
Esophageal adenocarcinoma	Proximal gastric mucosa (24)	↑	ELISA	[215]
Pulmonary dysfunction				
Asthma	Sputum (71)	↑	ELISA	[216]
Diabetes				
Type 2 DM	Plasma (10)	↔	ELISA	[217]
	Urine (10)	↑		
	Plasma (20)	↑	ELISA	[216]
	Plasma (21)	↑	LC-MS	[218]
	Urine (21)	↑		
	Plasma (8)	↔	GC-MS	[219]
	Plasma (40)	↑	GC-MS	[220]
	<i>Free</i>	↑		
	<i>Esterified</i>			
	Urine	↑		
	<i>15-F_{2c}-IsoP</i>	↑		
	<i>15-F_{2c}-IsoP-M</i>			
	Atherosclerotic plaques (5)	↓	GC-MS	[221]
Type 1 DM	Plasma (38)	↔	RIA	[222]
	Urine (38)	↔		
Metabolic syndrome	Plasma (10)	↑	ELISA	[223]
	Plasma (45)	↔	GC-MS	[224]
	<i>Free</i>	↔		
	<i>Esterified</i>			
	Urine	↔		
	<i>15-F_{2c}-IsoP</i>	↔		
	<i>15-F_{2c}-IsoP-M</i>			
Renal dysfunction				
Nephrotic syndrome	Plasma (14)	↔	GC-MS	[225]
	Urine (14)			
	<i>15-F_{2c}-IsoP</i>	↔		
	<i>2,3-dinor-8-iso-PGF_{2a}</i>	↔		
Chronic kidney disease	Plasma (60)	↑	GC-MS	[226]
	Plasma (184)	↑	GC-MS	[227]
	Plasma (87)	↔	GC-MS	[228]
Acute renal graft dysfunction	Serum (55)	↑	ELISA	[229]
Liver				
Biliary cirrhosis	Plasma (41)	↑	ELISA	[230]
	Urine (41)	↑		
Autoimmune hepatitis	Plasma (33)	↑	ELISA	[231]
	Urine (33)	↑		
Alcoholic liver disease	Plasma (24)	↑	ELISA	[232]
	Urine (24)	↑		
	Plasma (63)	↑	ELISA	[233]

Table 2 (continued)

Subjects	Sample	Disease vs control	Method	Reference
Non-alcoholic fatty liver disease	Plasma (90)	↑	ELISA	[233]
Others				
Thalassemia	Plasma (17)	↑	GC-MS	[234]
	Urine (17)	↑		
Dengue fever	Plasma (35)		GC-MS	[99]
	<i>Total</i>	↑		
	<i>Free</i>	↑		
	Urine (19)	↑		
Preeclampsia	Amniotic fluid (46)	↑	LC-MS	[235]
	Plasma-Maternal (23)	↔	GC-MS	[236]
	Plasma-Cord (23)	↔		
	Plasma (33)	↔	LC-MS/MS	[237]
	Plasma ⁺ (33)	↑		
Sepsis related to renal, hepatic, and coagulation failure	Plasma (15–19)	↑	GC-MS	[238]
Periodontal disease	Saliva (50)	↑	LC-MS/MS	[100]
Influenza A	Plasma (35)	↑	GC-MS	[239]
	Urine (35)	↔		
Oral lichen planus	Plasma (31)	↑	ELISA	[240]
Critically ill patients	Plasma (38)	↑	LC-MS/MS	[241]
Community acquired pneumonia	Serum (50)	↑	ELISA	[242]
Rheumatoid arthritis	Plasma (73)		LC-MS/MS	[243]
	<i>Free</i>	↓		
	<i>Esterified</i>	↑		
	Urine (73)	↑		
Paediatric sepsis	Plasma (42)	↑	ELISA	[244]
<i>Helicobacter pylori</i> infection	Exhaled breath condensate (41)	↑	ELISA	[245]

Annotations indicate ↑: increase, ↓ decrease and ↔ no change compared to controls. Numbers in the parentheses are the number of subjects in the study. ELISA: enzyme-linked immunosorbent assay; GC: gas chromatography; LC: liquid chromatography; MS: mass spectrometry.

such as the ones listed in Table 3. Most of these studies were reported within the last decade, showing that the detection of F₂-IsoPs is starting to receive significant attention in the environmental and marine science areas. Although not all treated marine fishes showed changes in the level of F₂-IsoPs in their samples, deep-frozen catfish, Fe³⁺-treated Fathead minnow fish, and H₂O₂-treated medaka fish consistently exhibited an elevation of F₂-IsoPs. Surprisingly, the abundance of F₂-IsoPs is reduced in baked salmon as compared to raw fish [104]. Hence, the use of F₂-IsoPs could also be an indication to the quality of lipids present. The feasibility of using F₂-IsoPs as a lipid quality indicator is especially important because fatty fishes constitute a large portion of healthy dietary lipids, and there is a risk falling ill if bad quality lipids are ingested. Of note, F₂-dihomo-IsoPs were also detected in the muscles of marine fish by Chung et al., but were not statistically different from normoxia and hypoxia treatments. However, hyperoxia-stressed medaka fish showed elevation of dihomooisofurans, which are produced from AdA non-enzymatically under higher oxygen tension [105].

In environmental stressor studies, F₂-IsoPs are elevated in human and animal subjects when exposed to air pollutants, such as wood smoke particles, ozone, fine particulate matter (PM_{2.5}), black carbon, and diesel exhaust. Other environmental contaminants also include formaldehyde, organophosphate insecticides, plasticizer, and perfluorooctanesulfonic acid (also an industrial contaminant). Collectively, the exact mechanism of action by these stressors to induce lipid peroxidation remains largely unknown, but has shown to cause discomfort and other complications along with oxidative stress. Remarkably, special attention should be paid to the potential role of 15-F_{2c}-IsoP as a wastewater biomarker for the assessment of community public health

Table 3
Isoprostanes and metabolites, and neuroprostanes detected in marine samples and environmental stressor related studies published up to 2016.

Study	Sample	Outcome	Method	Reference
Marine				
Arabian Gulf catfish and storage	Catfish gel: subcutaneous secretates	↑ -80 °C storage vs fresh samples.	GC-MS	[246]
Fathead minnow fish exposed to metal cations	Gill pavement cells	↑ In presence of Fe ³⁺ vs control; ↔ In presence of Pb ²⁺ vs control.	LC-MS	[247]
Atlantic Salmon from aquaculture and baking	Salmon meat	↓ Baking vs raw meat.	LC-MS/MS	[104]
Atlantic Salmon under chasing stress	Midgut and hindgut	↔ Acute chasing stress vs baseline.	LC-MS/MS	[248]
Zebrafish and hypoxia exposure	Brain	↔ F ₂ -IsoPs or F ₄ -NeuroP levels hypoxia vs control.	GC-MS	[249]
Medaka fish and hydrogen peroxide exposure	Body muscle	↑ F ₂ -IsoPs and metabolites, and F ₄ -NeuroPs levels for hydrogen peroxide exposed group vs control.	LC-MS/MS	[172]
Medaka fish under hypoxia and hyperoxia exposure	Body muscle	↔ F ₂ -IsoPs and metabolites, and F ₄ -NeuroPs levels for hypoxia or hyperoxia vs normoxia.	LC-MS/MS	[105]
Juvenile rainbow trout fed with selenium	Liver	↔ Before vs after feeding selenium.	ELISA	[250]
Farmed rainbow trout slaughtered by asphyxia or percussion	Plasma	↔ Asphyxia vs percussion slaughtering.	LC-MS/MS	[251]
Environmental stressor				
Exposure of wood smoke particles to healthy individuals	Urine	↑ Clean air vs wood smoke exposure.	RIA	[252]
Ozone exposure to healthy individuals	Plasma	↑ High ozone level vs normal level;	ELISA	[253]
Welders exposed to fine particulate matter (2.5)	Urine	↓ Acute ozone exposure after 4 h and then returned to baseline after 18 h.	ELISA	[254]
Adults with metabolic syndrome exposed to diesel exhaust	Urine	↓ Acute exposure but returned to baseline level after 24 h.	LC-MS/MS	[255]
Healthy subjects in living in Beijing, pre- and post air quality during the Olympics	Exhaled breath condensate	↔ Filtered air vs diesel exhaust.	ELISA	[256]
Home air quality and oxidative stress in children	Exhaled breath condensate	↑ Pre-Olympics; ↓ During-Olympics.	LC-MS/MS	[257]
Children exposure to black carbon over 2 different periods	Exhaled breath condensate	Fine particulate matter (2.5) and black carbon were associated to F ₂ -IsoPs, and black carbon was a bigger contributor for the increase.	ELISA	[258]
CD-1 Mice exposed to perfluorooctane sulfonate (PFOS) contaminant exposure	Liver, brain and kidney of pregnant dam and fetal mice	↔ Period 1 vs period 2 exposure. ↑ PFOS vs control in F ₂ -IsoPs and F ₄ -NeuroPs levels in liver of fetal mice; ↔ PFOS vs control in F ₂ -IsoPs and F ₄ -NeuroPs levels in brain of pregnant dam and fetal mice;	LC-MS/MS	[259]
Raw 24 h composite sewage	Sewage water	↑ PFOS vs control F ₂ -IsoPs levels in kidney of pregnant dam;	LC-MS/MS	[107]
Pregnant women exposed to formaldehyde and its effect on fetal growth	Urine	↔ PFOS vs control F ₂ -IsoPs levels in kidney of pregnant dam; ↑ PFOS vs control in F ₂ -IsoPs and F ₄ -NeuroPs levels in kidney of fetal mice. F ₂ -IsoPs was found in sewage samples.	ELISA	[260]
Organophosphate insecticides exposure to mice with idiopathic autism (BTBR T + tf/J)	Brain	No significant relationship was found with fetal growth and formaldehyde exposure. ↑ BTBR T + tf/J mice vs control.	ELISA	[261]
Bisphenol A disposal and correlation to human and sewage water	Sewage water and human urine	No association of human urinary F ₂ -IsoPs levels and Bisphenol A levels and levels of wastewater disposed.	ELISA	[262]
Framingham Heart Study Offspring and air pollution	Urine	Short term exposure to fine particulate matter (2.5) and sulphate was associated to urinary F ₂ -IsoPs	ELISA	[263]
Plasticizer exposure and couples seeking fertility treatment	Urine	Only 4 out of 16 phthalate plasticizers and non-plasticizers exposed to the couples were associated to urinary F ₂ -IsoPs.	ELISA	[264]
Coal miners in consecutive work shift exposed to methane (CH ₄), carbon dioxide (CO ₂), carbon monoxide (CO) and dimethyl sulphide gases	Exhale breath condensate	Two consecutive days of exposure to the gases had elevated F ₂ -IsoPs compared to those on first day (miners who had 5 days rest before work).	ELISA	[265]

Annotations indicate ↑ increase, ↓ decrease and ↔ no change compared to controls. IsoPs: isoprostane; NeuroP: neuroprostane; ELISA: enzyme-linked immunosorbent assay; GC: gas chromatography; LC: liquid chromatography; MS: mass spectrometry.

due to its high stability [106]. Recently, Ryu et al. have successfully detected 15-F_{2t}-IsoP in sewage samples [107] and found the levels to be associated with trans-3'-hydroxycotinine, a tobacco metabolite in the same samples [108]. While the concept of 15-F_{2t}-IsoP as the biomarker for community health assessment has only just been propositioned, the findings indicate tobacco smoking is habitual in the community of the sewage origin. Nevertheless, longer periods of monitoring are required to prove on its suitability as well as the stability in the sewage as it is highly exposed to microbial pathogens.

4.2. Phytoprostanes

PhytoPs are predominantly found in higher plants as mammals do not endogenously produce ALA due to the lack of delta-12 and delta-15 desaturases which are needed for the synthesis of essential fatty acids. Identified by Mueller and co-workers, they reported the presence of two series (9 and 16) of E₁-PhytoPs [19] and F₁-PhytoPs [109] from plant cultures. Other PhytoPs discovered include A₁-, B₁-, D₁-, and L₁-PhytoPs. Among which A₁- and B₁-PhytoPs are produced in low abundance in plants, where A₁-PhytoPs are readily isomerised into B₁-PhytoPs under extreme pH or high temperature. D₁- and F₁-PhytoPs are the most dominant PhytoPs in plants [110]. Plants constitutively produce ROS as signalling molecules for cell growth and development, but also significantly intensify PhytoP production under stress. Therefore, PhytoPs serve as an excellent biomarker for oxidative degradation of plant food. In addition, PhytoP can be esterified to galactolipid and was detected in *Arabidopsis thaliana* plant by Feussner's group [111].

The Gil-Izquierdo group has shown that PhytoPs of walnuts are sensitive biomarkers towards improper storage conditions (e.g. non-vacuum versus vacuum packed, and storing at 24 °C versus 4 °C) [112]. This suggests that the quality of plant oils could potentially be assessed by the measurement of PhytoPs. Also, Table 4 illustrates the wide variety of PhytoPs found in different plant samples, like peppermint leave, melon leave, almond cultivars, red wine, and dietary oils (e.g. sunflower, flaxseed, olive, soybean, rapeseed, walnut and grape seed oils). More importantly, olive oil being low in ALA showed the presence of F₁-PhytoPs in plasma and urine after consumption, but the biological activity to date, are not fully explored. Because Mediterranean diet contains high amount of extra virgin olive oil further investigation regarding the PhytoPs bioactivities is of great importance.

4.3. Neuroprostanes

The formation of neuroprostanes (NeuroPs) proceeds via the non-enzymatic oxygenation of DHA. They are widely used as a specific biomarker for oxidative damage of brain tissues. Clinical and experimental results in human and animal models consistently showed that oxidative damage to the brain induces an increment of F₄-NeuroPs production as depicted in Table 5. Interestingly, studies which measured different series of F₄-NeuroPs showed that 10-F_{4t}-NeuroP, but rarely 4-F_{4t}-NeuroP, was found in the urine samples. Probably, this implies that the excretion of 10-F_{4t}-NeuroP might be subjected to further metabolism.

In some studies, A₄/J₄-NeuroPs were similarly elevated from ROS insult. For example, rats exposed to alcohol [113] and in tick-borne encephalitis patients [114] had higher amounts of A₄/J₄-NeuroPs compared to control group brain tissue and plasma, respectively. Apparently, F₄-NeuroPs appears to be a more suitable biomarker for neurodegeneration and brain injury, including the Rett Syndrome and ischemic-stroke, compared to F₂-IsoPs. The advancement of quantifying F₄-NeuroPs clinically for early detection of debilitating neurological disorders has been slow, mostly due to the lack of commercially available standards for human testing. Currently, only a handful of studies were conducted in neurodegenerative disease patients, and more work is required to fully understand their biological role in these diseases.

In summary, F₄-NeuroPs continue to serve as a reliable biomarker for brain oxidative damages, but whether the correlation of brain F₄-NeuroPs and plasma or urine F₄-NeuroPs can be established for an early detection of neurological disorder, such as neurodegenerative diseases, requires further experimental data.

5. Bioactivities of isoprostanoids

In addition to their application as biomarkers of oxidative stress, isoprostanoids were reported to exert biological activities. They serve as homeostatic mediators in keeping physiological functions, or involve in inflammation and immunity that are associated to the pathology of diseases. The following section reviews the current knowledge of the bioactivities of isoprostanoids, namely IsoPs, NeuroPs and PhytoPs.

5.1. Isoprostanes

AA derived 15-F_{2t}-IsoP was initially found to be a potent renal vasoconstrictor in the low nanomolar range [115]. In subsequent studies of 15-F_{2t}-IsoP, a similar constriction effect was observed in the vascular systems such as the liver, heart, lung [116,117], smooth muscle [2] and retina [118], in peripheral lymphatics [119] and the airways [120]. Other biological activities of 15-F_{2t}-IsoP also include inhibition of angiogenesis [121] and modulation of glutamate release from the bovine retinae [122]. The biological activities of 15-F_{2t}-IsoP are generally thought to be exerted as an agonist for the activation of thromboxane receptors (TPR), that can be abrogated by the TPR antagonist SQ29548 [115,116,123]. Interestingly, unlike other TPR ligands, e.g. thromboxane A₂, the binding mechanism of 15-F_{2t}-IsoP to the active site of the platelet TPRs revealed a unique coordination profile as studied by site-directed mutagenesis. While Phe¹⁸⁴ and Asp¹⁹³ are shared among 15-F_{2t}-IsoP and other TPR ligands, the binding of 15-F_{2t}-IsoP to TPRs requires an additional interaction with Phe¹⁹⁶ [124]. In the same study, the second 15-F_{2t}-IsoP binding site on platelet was identified which constitutes to a total opposite effect. This was realised via an unknown cAMP-coupled receptor that inhibits the activation of platelet [124]. Therefore, the biological activities of 15-F_{2t}-IsoP can be platelet activating or inhibiting, depending on of the active sites that is occupied. Nonetheless, not all F₂-IsoPs are homogenous in their bioactivity and mode of actions. For example, 15-F_{2c}-IsoP activates the PGF_{2α} receptor at high concentration and induces hypertrophy of cardiomyocytes via intracellular signalling pathways different from those of PGF_{2α} [125,126]. Also, 5-F_{2t}-IsoP, another abundantly generated F₂-IsoP isomer analogous to 15-F_{2t}-IsoP, showed no vasomotor activity [127,128]. Exploration into the bioactivity of 12- and 8-series F₂-IsoPs has been limited largely due to the low abundance *in vivo*, except for one study that revealed 12-F_{2t}-IsoP and its epimer, 12-*epi*-12-F_{2t}-IsoP, induced pig retinal and brain vasoconstriction in a dose-dependent manner [128].

In addition to F₂-IsoPs exhibiting biological activities, arachidonic acid-derived E-ring IsoPs were widely studied. For instance, 15-E_{2t}-IsoP, one of the two IsoPs (together with 15-F_{2t}-IsoP) that was available for biological testing in the early years, has shown to be a renal vasoconstrictor that caused a reduction in the glomerular capillary pressure and filtration rate at low nanomolar range [129]. This 15-E_{2t}-IsoP was even more potent than 15-F_{2t}-IsoP in activation of TP and EP₃ receptors [130,131]. Furthermore, 15-E_{2t}-IsoP has been reported to activate intestinal epithelial cells contraction [132], stimulate the binding of monocytes to the endothelial cells [133], exert contractile activity on gastrointestinal smooth muscle [134] and act as a regulator of the airways [135,136]. In contrast, the analogous 15-D₂-IsoP has received less attention while its chemical total synthesis has been described but being rather an instable compound [137].

While D₂- and E₂-IsoPs are not the final metabolites of the AA peroxidation pathway, they are subjected to dehydration for the formation of J₂- and A₂-IsoP, respectively. Since the depiction of A₂- [47]

Table 4
Phytosteranes identified in plants food and algae.

Study	Sample	Type	Outcome	Method	Reference
Characterization of F ₁ -PhytoP, E ₁ -PhytoP	Peppermint leave	F ₁ -PhytoP, E ₁ -PhytoP	↑ Esterified F ₁ -PhytoP vs free F ₁ -PhytoP.	GC-MS	[266]
Measurement of plant oils, and urine after plant oil ingestion (WO) and grape seed (GO) oils	Olive (OO), linseed (LO), soybean (SO), rapeseed (RO), walnut (WO) and grape seed (GO) oils	A ₁ -, B ₁ -, E ₁ -, F ₁ -PhytoP	LO had the highest A ₁ - and B ₁ -PhytoP levels; SO and LO had the highest E ₁ -PhytoP level; LO and SO had the highest F ₁ -PhytoP levels; A ₁ - and E ₁ -PhytoPs were not detectable in urine and plasma; No detection of urinary F ₁ -PhytoP before plant oil intake in plasma and urine; F ₁ -PhytoP in plasma was below detection level; ↑ F ₁ -PhytoP in urine before vs after SO or OO; ↔ F ₁ -PhytoP in urine before vs after GO; F ₁ -PhytoP metabolism very slow.	GC-MS	[8]
Flaxseed oil (FO) or olive oil (OO) supplementation to healthy men	Plasma and urine	F ₁ -PhytoP	↑ In plasma FO group vs OO group; ↔ In urine FO group vs OO group.	GC-MS	[267]
Identification of PhytoPs in macroalgae	Three types of chlorophyta, sixteen types of phaeophyta, and five types of rhodophyta	B ₁ -, F ₁ -, L ₁ -PhytoP	F ₁ - and L ₁ -PhytoP were predominant in two microalgae type; F ₁ -PhytoP level was high in brown microalgae.	LC-MS/MS	[180]
Almond cultivars grown under rain-fed and conventional conditions or ecological conditions, and irrigation	Eleven types of almond cultivars	B ₁ -, D ₁ -, F ₁ -PhytoP	F ₁ -PhytoP was predominantly found in the almonds; L ₁ -PhytoP minor amount was found	LC-MS/MS	[268]
Extra virgin olive oil (EVOO) in relevance to olive fruit pit hardening by the control of water irrigation	EVOO	B ₁ -, D ₁ -, F ₁ -, L ₁ -PhytoP	D ₁ -PhytoP was found in two type of almonds; ↑ D ₁ -PhytoP levels in ecological conditions; ↓ Total PhytoPs Rain-fed vs irrigation grown almonds. ↑ EVOO from water deficit in olive fruit compared to controls;	LC-MS/MS	[268]
Extra virgin olive oil (EVOO) from regulated deficit irrigation (RDI) olive fruit and seasonal change	EVOO	B ₁ -, D ₁ -, F ₁ -, L ₁ -PhytoP	B ₁ - and F ₁ -PhytoPs are potential biomarker to assess water stress in olive tree.	LC-MS/MS	[268]
Measurement of PhytoPs in commercial oils	Extra virgin olive oil (EVOO), olive oil (OO) and refined sunflower oil (SO)	B ₁ -, D ₁ -, F ₁ -, L ₁ -PhytoP	↑ All PhytoPs in EVOO from RDI plants. SO had 20-fold higher total PhytoPs than EVOO and 8-fold higher than OO;	LC-MS/MS	[268]
Measurement of PhytoPs in red wine	Carbonic maceration wine (CMW) and must (CMM), aged wine (AW) and must (AM), high expression wine (HEW) and must (HEM)	B ₁ -, D ₁ -, F ₁ -, L ₁ -PhytoP	SO had concentrated amount of all 7 types of PhytoPs, and low amounts of 4 types in EVOO and 3 types in OO only	LC-MS/MS	[269]
Almond processing, packaging and storage	Different almond cultivars	B ₁ -, D ₁ -, F ₁ -, L ₁ -PhytoP	F ₁ -PhytoPs concentrated in all class D ₁ -PhytoPs levels was approximately 100-folds higher in the HEM compared to other class. All types of PhytoPs were found in HEM only F ₁ -PhytoPs levels was the highest in all cultivars; Total PhytoPs levels was higher in almonds packed in non-vacuumed materials compared to vacuumed; Almonds stored at 24 °C had higher PhytoPs compared to 4 °C;	LC-MS/MS	[112]
Thermal stress and antioxidant effect in melon plants	Melon leaves	B ₁ -, F ₁ -, L ₁ -PhytoP	Raw almonds had the highest total PhytoPs compared to fried-salt and roasted. Thermal stress increased PhytoPs levels compared to non-stressed; Antioxidant treatment reduced PhytoPs levels in stressed leaves compared to non-stressed.	LC-MS/MS	[181]

Annotations indicate ↑ increase, ↓ decrease and ↔ no change compared to controls. PhytoP: phytosterane; GC: gas chromatography; LC: liquid chromatography; MS: mass spectrometry.

Table 5Neuroprostanes (F₄-NeuroPs and A₄/J₄-neuroprostanes) identified and/or used as biomarkers and to indicate human disease status related to oxidative stress published up to 2016.

Study	Sample	Outcome	Method	Reference
Biological studies				
Oxidative damage to brain by kainic acid	Rat cerebrum	↑ After 2 h injection;	GC-MS	[180]
Characterization of NeuroPs using rat model	Rat urine	↔ From baseline after injection.		
	Liver treated with CCl ₄	↑ 4- and 10-series NeuroPs were elevated in the liver;	LC-MS	[23]
	Brain	NeuroPs were identified in brain.	GC-MS	
Mice supplemented with fish oil (FO) and induced with or without inflammation	Lung	↑ FO vs control; ↑ FO + inflammation vs FO.	GC-MS	[270]
Zebrafish under hypoxia	Brain	↔ Before vs after hypoxia.	GC-MS	[249]
Sonoporation of Jurkat cells	Cells	↔ Sonoporated vs non-sonoporated.	LC-MS/MS	[72]
Rats fed with alcohol with or without sweet grass (antioxidant) beverage	Brain ^a	↑ Alcohol vs control; ↔ Sweet grass vs control; ↔ Alcohol + sweet grass vs control; ↓ Alcohol + sweet grass vs alcohol.	LC-MS/MS	[113]
Rats liver injury by CCl ₄ and supplemented with high fat diet of extra virgin olive oil (EVOO) or corn oil (CO) or lard	Liver	↑ EVOO, CO, lard vs control; ↓ EVOO + CCl ₄ group vs CCl ₄ group; ↔ CO + CCl ₄ or lard + CCl ₄ group vs CCl ₄ group.	LC-MS/MS	[271]
Human studies				
Healthy and smoker volunteers	Plasma	↑ Smokers' vs healthy; ↑ Smokers after cigarette smoking.	GC-MS	[272]
Healthy controls and ischemic-stroke patients	Plasma	↑ Ischemic-stroke vs control.	GC-MS	[273]
Type 2 diabetic patients with or without zinc supplementation	Plasma	↑ Diabetic vs non-diabetic controls; ↔ Diabetic placebo supplementation vs diabetic zinc supplementation.	GC-MS	[220]
Normal pregnancy and pre-eclampsia pregnancy	Maternal and cord blood plasma	↑ Maternal plasma normal vs eclampsia; ↑ Cord plasma normal vs eclampsia.	GC-MS	[236]
Female Rett syndrome patients with or without fish oil	Plasma	↓ Before vs after fish oil supplementation.	GC-MS/MS	[65]
Influenza A patients and healthy controls	Plasma	↔ Acute illness vs control; ↓ Acute illness vs 3 months post illness.	GC-MS	[239]
Mild Alzheimer's disease (AD), amnesic mild cognitive impairment (a-MCI) and healthy control	CSF	↔ AD or a-MCI vs control; ↔ AD vs a-MCI.	GC-MS	[184]
Female patients with <i>MECP2</i> gene and Rett syndrome patients with typical presentation, supplemented with or without fish oil	Plasma	↑ Rett patients vs healthy controls; ↓ Rett patients before vs after supplementation.	GC-MS/MS	[274]
Preterm infants with bronchopulmonary dysplasia (BPD)	Urine	↔ BPD vs control throughout 4 weeks gestation.	LC-MS/MS	[275]
Epilepsy and control	Urine	↔ Epileptic group vs control.	LC-MS/MS	[102]
Rett syndrome patients and healthy controls	Skin fibroblast	↑ RTT patients vs control.	GC-MS/MS	[276]
Traumatic brain injury (TBI) and controls	CSF	↑ TBI patients post-operation vs control.	GC-MS	[191]
Tick-borne encephalitis (TBE) patients and healthy subjects	Plasma ^a	↑ TBE vs control.	LC-MS/MS	[114]
Athletes in altitude training (hypoxia)	Urine	↑ Before vs after training.	LC-MS/MS	[277]
Neuroborreliosis (NB) patients and antibiotics treatment	Urine, plasma, CSF	↑ NB vs control in CSF and plasma; ↓ Before vs after in NB CSF and plasma; Urine levels were not detectable.	LC-MS/MS	[200]
Down syndromes and controls	Plasma	↑ Down syndrome vs control.	GC-MS/MS	[278]
Healthy females before and after wine intake	Urine	↓ Before vs after and postulated to be due to phenolic compound, hydroxytyrosol.	LC-MS/MS	[279]
Epilepsy and new generation drug treatment	Urine	↔ Epileptic patient vs control; ↑ Epileptic patient or control vs epileptic patients with new-generation antiepileptic drugs.	LC-MS/MS	[280]
<i>MECP2</i> Duplication Syndrome (MDSS), Rett syndrome patients and control	Plasma	↑ MDS or Rett vs Control; ↔ MDS vs Rett.	GC-MS/MS	[281]

^a Annotation indicates A₄/J₄-neuroprostanes, otherwise it is F₄-neuroprostanes. Arrows indicate ↑ increase, ↓ decrease and ↔ no change compared to controls. PhytoP: phytoprostane; GC: gas chromatography; LC: liquid chromatography; MS: mass spectrometry.

and J₂-IsoPs [48], their total syntheses and biological activities were investigated extensively. For example, Musiek et al. reported that 15-A_{2t}-IsoP induced caspase-3 cleavage, leading to apoptosis in the cortical cultures at sub-micromolar concentrations [138]. Conversely, anti-inflammatory effects of 15-A₂-IsoPs were also reported by inhibition of the NF-κB pathway in lipopolysaccharide (LPS)-induced macrophages [139] and human gestational tissues [140]. Further, it was mentioned that 15-J₂-IsoPs, but not 15-A₂-IsoPs, inhibited inflammatory response via the PPARγ activation and induced RAW264.7 cells apoptosis in a PPARγ-independent manner [139].

In comparison to 15-F_{2t}-IsoPs, EPA-derived IsoPs were discovered only about a decade ago and rendered as one of the least studied IsoPs. Although 5- and 18-series F_{3t}-IsoPs are theoretically predominant over other regioisomers [141], no accounts on the bioactivity of 18-F_{3t}-IsoPs have been reported. The 5-F_{3t}-IsoPs was able to modulate the release of neurotransmitters in isolated bovine retina [142]. One report on the

bioactivity of F₃-IsoPs by Brooks et al. 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 [143]. Moreover, Gao et al. reported that 15-J₃-IsoPs induced Nrf2 expression by inhibiting its negative regulator Keap1 [144].

5.2. Phytoprostanes

Although the primary source of PhytoPs comes from plants, this section reviews their biological activities when exposed to humans. Uptake of PhytoPs in humans is predominantly through ALA-enriched diets because we do not endogenously synthesize ALA. High levels of F₁-, E₁-, A₁- and B₁-PhytoPs have been found in vegetable oils with the concentration ranging from 0.09 to 99 mg/L [8]. In the same study, Karg et al. reported that A₁-PhytoPs, and B₁-PhytoPs to a lesser extent,

inhibited dose-dependently NF- κ B transactivation in transfected HEK 293 and LPS-activated RAW264.7 cells [8]. Also, it was reported that A₁-PhytoPs, but not B₁-PhytoPs, induced apoptosis in Jurkat T-cells [8]. An alternative exposure to PhytoPs is through the inhalation of pollen, of which E₁-PhytoPs are the most abundant. Studies on human dendritic cells showed that E₁-PhytoPs inhibited LPS-induced interleukin (IL)-12 production and enhanced T-helper 2 cell polarization [145] via a PPAR γ -dependent mechanism [146]. Recently, the study of PhytoPs has been extended to cells from the central nervous system. Minghetti and co-workers demonstrated B₁-PhytoPs to be neuroprotective for undifferentiated, but not differentiated, SH-SY5Y cells from H₂O₂ insult, and promoted oligodendrocyte differentiation partly via PPAR γ activation [9]. To date, despite the availability of F₁-PhytoPs chemical standards [51], information about their biological activity in mammals is still missing, and they remain biomarkers for oxidative damage to plants.

5.3. Neuroprostanes

Within the regioisomers of NeuroPs, the 4- and 20-series NeuroPs are the most abundant form of NeuroPs while, the other type can be further oxidized. Some of the NeuroP compounds and internal standards were successfully synthesized by the groups of Vidari-Zanoni [147], Taber [148] and Durand [149–151]. Remarkably, elevation of F₄-NeuroPs was detected in the brain tissue of patients with neurodegenerative diseases like Alzheimer's diseases (AD) and hence it has been recognised as a reliable biomarker for neural oxidative damage. The first study on the bioactivity of NeuroP used 14-A₄-NeuroPs by Musiek and colleagues described 14-A₄-NeuroPs as a potent anti-inflammatory mediator, inhibiting NF- κ B activation in LPS-induced macrophages [152]. Similarly, Majkova et al. showed that A₄/J₄-NeuroPs, prepared from DHA, to down-regulate PCB77-induced monocyte chemo-attractant protein-1 expression and Nrf2 activation in primary pulmonary endothelial cells [153]. It is worth noting that IsoPs/PhytoPs/NeuroPs with A- or J-ring structure displayed anti-inflammatory effects, primarily via the inhibition of NF- κ B pathways with or without the activation of PPAR γ , whereas F-ring isoprostanooids consistently failed to exhibit any beneficial effects in these models. Nevertheless, 4(RS)-4-F_{4t}-NeuroP has recently displayed cardiac anti-arrhythmic properties *in vitro* and *in vivo* via the protection of the ryanodine receptor [6]. In another follow up study by the same group, 4(RS)-4-F_{4t}-NeuroP has shown to protect ischemia-reperfusion damages by down-regulating the release of cytochrome c and caspase 3 activity [7]. In addition, 4(RS)-4-F_{4t}-NeuroP exerted anti-proliferative effects in the human breast cancer cell line (MDA-MB-231), and even more potently when encapsulated in poly- ϵ -caprolactone (P ϵ CL) nanocapsules [154]. More recently, the anti-inflammatory effects of 4(RS)-4-F_{4t}-NeuroP and 14-A_{4t}-NeuroP were compared with the well-known enzymatically derived anti-inflammatory lipid mediators NDP1 and PDX. The result suggested cyclopentenone NeuroPs or F-type NeuroP i.e. 4(RS)-4-F_{4t}-NeuroP and 14-A_{4t}-NeuroP possess anti-inflammatory activities similar to the protectins in human macrophages [155]. Consequently, 4(RS)-4-F_{4t}-NeuroP is the very first F-ring isoprostanooid compound to show bioactivities in mammalian cells, this could potentially be extrapolated into other cell types and species. This gives rise to the question whether the elevated amount of F₄-NeuroPs in AD patients is the cause or the consequence of neurodegenerative diseases, and if these F₄-NeuroPs play a role in diseases regulation.

6. Outlook and conclusions

Insofar, isoprostanooids have generally been used as biomarkers of oxidative damage in mammalian diseases or for plant injuries. Only for 15-F_{2t}-IsoP, metabolism and excretion has been described. However, the use of isoprostanooids as oxidative stress biomarkers in general has suffered largely from the misconception that a single isomer is suitable

to reflect oxidative damage. Obviously, different cells and tissues have different PUFA composition and content. In turn, specific isoprostanooids should serve as tissue and cell specific oxidative stress markers. For example, 15-F_{2t}-IsoP might reflect blood related oxidative injury of peripheral cells and tissue, while the 4-F_{4t}-NeuroPs needs to be investigated when concerning neurological conditions. Furthermore, it was shown that isoprostanooids originating from n-3 PUFA have biological activities. Although more research needs to be conducted, protective mechanisms from muscle injuries to cancer have been described. Frequently the limitation for more detailed studies is the lack of pure compounds. This also limits the validation of analytical methods, where poor availability of the unique isoprostanooids restricts quantitative measurements. However, with the precursor and transition ions published here, and mass spectrometry spectra for LC-MS/MS, at least one can undertake qualitative evaluation of the isoprostanooids.

No doubt, there are much needs to understand about the role of isoprostanooids in marine biology. Despite being abundant in PUFA, little is known about isoprostanooids and their physiological and biological presence in marine organisms. Further, due to climate change and environmental pollution, isoprostanooids are probably released in PUFA rich marine species; whether they are detrimental or beneficial in reproduction and development is unknown.

Further, using the appropriate isoprostanooids, large human population studies need to be conducted using mass spectrometry based analysis to warrant specificity, ultimately allowing a final assessment of the usefulness of the isoprostanooids as specific oxidative damage markers [156]. Additionally, isoprostanooids such as dihom-IsoPs and NeuroPs may be characteristic for white and grey matter damage respectively possibly presenting diseases specific biomarkers.

This review presents a comprehensive overview of isoprostanooid chemistry and biology over the past three decades hopefully helping the community to understand the role of these non-enzymatic PUFA derivatives in health and disease.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.plipres.2017.09.004>.

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