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Review

The novelty of phytofurans, isofurans, dihomo-isofurans and neurofurans: Discovery, synthesis and potential application

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ABSTRACT

Polyunsaturated fatty acids (PUFA) are oxidized *in vivo* under oxidative stress through free radical pathway and release cyclic oxygenated metabolites, which are commonly classified as isoprostanes and isofurans. The discovery of isoprostanes goes back twenty-five years compared to fifteen years for isofurans, and great many are discovered. The biosynthesis, the nomenclature, the chemical synthesis of furanoids from α-linolenic acid (ALA, C18:3 n-3), arachidonic acid (AA, C20:4 n-6), adrenic acid (AdA, 22:4 n-6) and docosahexaenoic acid (DHA, 22:6 n-3) as well as their identification and implication in biological systems are highlighted in this review.

Contents

1. Introduction

Reactive oxygen species (ROS) are free radicals generated under physiological conditions, but also under the so-called oxidative

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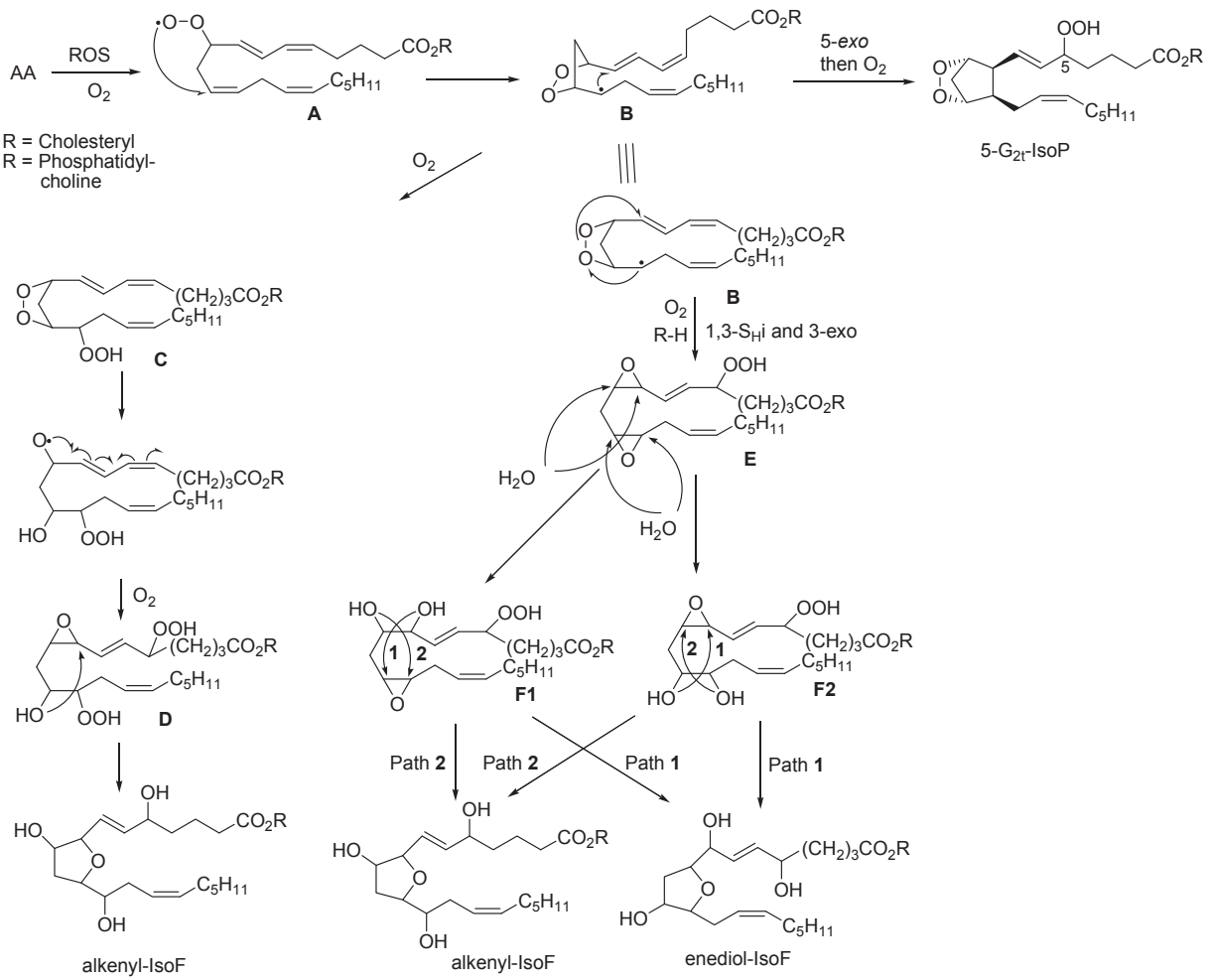
stress condition (OS) when natural antioxidant defences are overwhelmed by the amount of ROS generated. ROS target oxidation prone polyunsaturated fatty acids (PUFA) to undergo lipid peroxidation (LPO) [1]. The hydroxyl radical (•OH) is believed to be the most reactive radical *in vivo*, however other radicals can also participate in the processes of LPO [2]. However, no contentious exists if ROS can be specific of certain lipid and therefore of certain type of oxygenated metabolites. Furthermore, it is also believed that the non-enzymatic free radical mechanism of LPO that occurs in three phases (initiation, propagation, termination) could be more subtle than anticipated [3,4]. OS and LPO have been clearly associated to several pathologies and diseases, and one particular biomarker of OS was discovered in the nineties and called F_2-isoprostanes (F_2-IsoPs). They are generated from autooxidation of arachidonic acid bounded phospholipid (AA, C20:4 n-6) and are circulating in biological fluids as free form mainly. Today they are currently considered as the best marker of OS in biological systems. In the biosynthesis route of IsoPs, an endoperoxide carbon radical (B) undergoes a 5-*exo*-trig cyclization to form the cyclopentane ring of IsoPs [5,6] (Scheme 1). However, at high oxygen tension further transformations can occur and oxygen molecule may react with the endoperoxyde carbon radical to generated tetrahydrofuran ring containing compounds. Those new metabolites were termed isofurans (IsoFs). This second route may prevent the IsoPs pathway and limit their formation [7]. It is thus reasonable to measure IsoFs in addition to IsoPs in the case of high oxygen tension injury e.g. hyperoxia, ischemia-reperfusion etc. Depending on the parent PUFA that at least would possess two skipped diene units (i.e; three alkenes separated by a CH_2), other furanoid metabolites can be formed and were discovered in human tissues or fluids e.g. neurofurans (NeuroFs) from docosahexaenoic acid (DHA, 22:6 n-3), dihomo-isofurans (dihomo-IsoFs) from adrenic acid (AdA) and in plants like the phytofurans (PhytoFs) from α-linolenic acid (ALA, C18:3 n-3). Those metabolites should be added to the list of metabolites to quantitate OS. The present review aims to provide a concise overview on these furanic PUFA metabolites, from how they are formed *in vivo* and how they are named. We also would like to highlight that these metabolites are not commercially available and need to be prepared by organic chemists before being evaluated. Accordingly, the syntheses developed until now will be presented. Finally, the last part will be focused on the identification of those metabolites and their implication in biological systems. More importantly, this review will also give keys to the researchers in the preparation of the samples and the measurements of such metabolites.

2. Biosynthesis

In 1990, Morrow and co-workers revealed the formation of IsoPs from arachidonic acid esterified as phospholipid, and explained their formation via a radical initiated mechanism [5]. Hydrogen abstraction of the bis-allylic hydrogen atom of AA ester lead to



Scheme 1. Mechanistic explanation for the formation of IsoPs and IsoFs (only one isomer of one series is shown).

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