PERSPECTIVE

Diterpenes and the crosstalk with the arachidonic acid pathways, relevance in neurodegeneration

Dementia has emerged as one of the main threats to human health in the modern civilization. Increased aging of world population and unhealthy lifestyle habits have been identified as critical factors able to facilitate dementia establishment. In this context, according to the Alzheimer's Research International, Alzheimer's disease (AD) constitutes the primary cause of dementia worldwide and its numbers are expected to grow during the following years. Clinically, AD is characterized by the progressive decline in the cognitive performance as well as by an altered social behavior. Initially affecting the short-term memory, the long-term memory becomes compromised as the pathology progresses. Relevantly, the severe cognitive impairment observed in AD reflects the dramatic effects of the pathology to the hippocampus and to the brain cortex circuitry, characterized by synaptic damage and neuronal loss. Histopathologically, AD displays two pathognomonic lesions within the brain parenchyma: the extraneuronal senile plaques, which are constituted by aggregated forms of the amyloid-β (Aβ) peptide, and the intraneuronal formation of neurofibrillary tangles (NFTs), constituted mainly of hyperphosphorylated tau protein. As reported elsewhere, it is important to note that additional features develop during AD, playing a critical role in its pathophysiology. Severe neuroinflammation, represented by glial reactivity and increased levels of pro-inflammatory mediators, vascular disease, mitochondrial dysfunction, calcium dyshomeostasis, and oxidative stress, are some of the most relevant alterations observed during AD. Regrettably, despite significant resources committed to the study of AD, no effective therapy is currently available to improve patient's outcome. Thus, the evaluation of potentially useful molecules able to modulate the progression of the disease remains an urgent need to be satisfied in the context of AD research.

Among the different molecules under study, terpenoids, and specifically diterpenes (DPs), have demonstrated significant beneficial effects regarding the several features developed during the neurodegenerative process, particularly AD. Indeed, several groups which have evaluated the potentialities of traditional herbs against chronic-degenerative disorders have found that different DPs representatives accounts for the beneficial effects observed in some cancer models and against some viral and bacterial infections (Islam et al., 2016). Relevantly, our lab, in agreement with other research group, has evidenced that ANDRO, a labdane diterpene obtained from the *Andrographis paniculata*, improves several AD related alterations, such as cognitive impairment, neuroinflammation, synaptic protein loss, and long-term potentiation (LTP) capability, in both the double transgenic APPswe/PS1 mice and the *Octodon degus*, a spontaneous AD-like model (Rivera et al., 2016). Interestingly, several of these effects were linked to the direct activity of ANDRO on the activation of the canonical Wnt signaling pathway, specifically, because of the inhibition of the glycogen synthase kinase-3 activity, allowing the accumulation of β-catenin in the cytoplasm and its subsequent translocation to the cell nucleus to induce Wnt target genes expression (Tapia-Rojas et al., 2015). More recently, we have evaluated the neurobiological and neuroprotective effects of ferruginol, jatrophone and junicedric acid, three DPs obtained from the *Prumnopitys andina*, *Jatropha isabelli*, and *Araucaria araucana*, respectively (Zolezzi et al., 2018). These DPs demonstrated to prevent the Aβ-mediated neurodegeneration, to prevent the synaptic protein loss, to induce LTP, to activate calcium dependent kinases, and to modulate the expression and/or activation of Wnt signaling components. Relevantly, even though the wide spectrum of beneficial effects observed for DPs, the mechanisms of action and/or the interaction with different molecular pathways within the cells remain poorly explored, limiting our understanding of the usefulness of the DPs in the context of neurodegeneration.

Although inhibition of the nuclear factor-κB pathway has been described among the anti-inflammatory effects of the DPs, it has been demonstrated that these molecules can block the metabolism of the arachidonic acid (AA) preventing the formation and release of several eicosanoids able to induce the inflammatory reaction. In this regard, some DPs can prevent the formation of AA from the membrane phospholipids by inhibiting the phospholipase-2 (Tran et al., 2017). Additionally, these molecules can inhibit the cyclooxygenase (COX) as well as the lipoxygenase (LOX), reducing significantly the levels of proinflammatory mediators, such as prostaglandins and leukotrienes (Tran et al., 2017). Thus, DPs will not act only preventing the formation of AA, the substrate of the COX and LOX, but to directly blocking the enzymes responsible for the formation of the final AA-effectors. Notably, the same situation has been observed regarding the AA-monooxygenase pathway. This additional AA-metabolic cascade, which possesses two branches the AA-ω-hydroxylase (mainly represented by the CYP4 members of the CYP450) and the AA-epoxygenase (mainly represented by the CYP2 members of the CYP450) (Capdevilla and Falck, 2018), have demonstrated to be blocked by some representatives of the DPs family including ANDRO (Pekthong et al., 2009). Interestingly, the blockade of the CYP2 members by means of the DPs might help to explain some of the undesirable effects reported for this family of compounds. Indeed, while the hydroxylase products, termed hydroxyeicosatetraenoic acids, have demonstrated detrimental effects in several biological systems; on the contrary, the epoxygenase products, named epoxyeicosatrienoic acids (EETs), have been related with cell proliferation and migration, inflammatory modulation, as well as with protection of the heart, liver, kidney and relevant vascular functions (Capdevilla and Falck, 2018). Then, the blockade of the EETs might result in the loss of these activities, leading to increased vulnerability of some organs and/or loss of inflammatory control.

In this regard, several members of the CYP2 are present in the brain, suggesting the local production of the EETs. Notably, it has been demonstrated that the glutamate stimulation induces the EETs production by the astrocytes in a CYP2J mediated manner, while Aβ exposure causes the decrease of the EETs levels within the brain (Liu et al., 2017). Similarly, it has been also shown that exogenous EETs can preserve the mitochondrial function within the astrocytes even in the presence of the Aβ (Sarkar et al., 2014). Additionally, some reports have also linked the activity of the EETs with the increased activity of the Wnt signaling and some nuclear receptor superfamily, specifically the peroxisome proliferator-activated receptors, which independently have systematically demonstrated to exert beneficial effects in the context of neurodegeneration. Remarkably, strategies based in the upregulation of the EETs levels have demonstrated to be able to induce LTP within the hippocampus (Wu et al., 2017). These findings seem to clearly demonstrate that the EETs are involved in the proper functioning of the brain and that the reduction of the EETs levels can be related with the development of pathological processes including neurodegenerative disorders, such as AD.

Considering the DPs-induced modulatory activity on the different branches of the metabolism of the AA, it is possible to suggest that even when DPs can exert highly relevant beneficial effects in the context of neurodegeneration; it will, concomi-

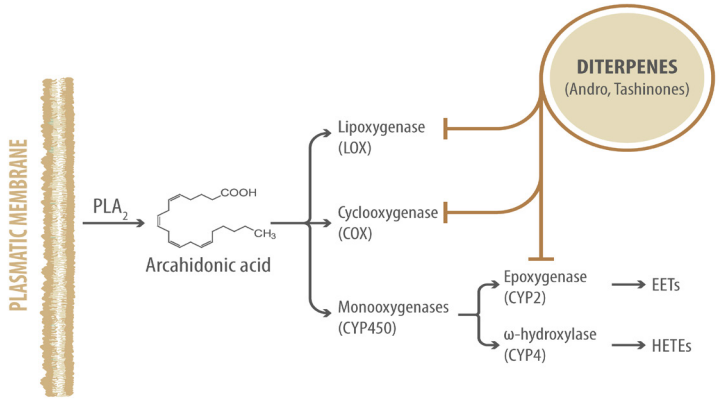

Figure 1 Suggested modulatory effects of DPs on the arachidonic acid metabolism.
Scientific evidence suggests that different members of the family of compounds can exert relevant actions on the metabolism of the arachidonic acid. In this regard, it has been demonstrated that some DPs can block the PLA_2 blocking the formation of arachidonic acid, preventing the subsequent synthesis of inflammatory mediators. Similarly, DPs can inhibit the activity of LOX and COX further stopping the release of inflammatory mediators. Relevantly, a new and complementary inhibitory effect recently described for the DPs is they activity on some members of the monooxygenase family of enzymes. Particularly, evidence suggests that DPs can block the epoxygenase (cytochrome P450 2, CYP2) causing an inhibitory effect on the synthesis of EETs which have demonstrated relevant beneficial effects on different cellular systems including the neurons. DPs: Diterpenes; PLA_2: phospholipase A2; EETs: epoxyeicosatrienoic acids; HETEs: hydroxyeicosatetraenoic acids.

tantly, have a negative impact on the levels of EETs (**Figure 1**). Therefore, it is possible to theorize that the combined administration of some DPs representatives, such as andrographolide, ferruginol or jatrophone, together with synthetic EETs, might enhance the neuroprotective effects observed by these molecules individually. In this regard, it is expected that future therapeutical alternatives against AD addresses some of the different molecular events common to AD; thus, the potentialities of a synergistic effect between DPs and EETs might constitute a novel approach to identify new potential pharmacological targets against neurodegeneration and should open a new field of research aimed to exploit the already known beneficial effects of DPs, avoiding the detrimental effects commonly reported for this family of compounds.

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