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Review article

Comprehensive review on the interaction between natural compounds and brain receptors: Benefits and toxicity

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ABSTRACT

Given their therapeutic activity, natural products have been used in traditional medicines throughout the centuries. The growing interest of the scientific community in phytopharmaceuticals, and more recently in marine products, has resulted in a significant number of research efforts towards understanding their effect in the treatment of neurodegenerative diseases, such as Alzheimer's (AD), Parkinson (PD) and Huntington (HD). Several studies have shown that many of the primary and secondary metabolites of plants, marine organisms and others, have high affinities for various brain receptors and may play a crucial role in the treatment of diseases affecting the central nervous system (CNS) in mammalians. Actually, such compounds may act on the brain receptors either by agonism, antagonism, allosteric modulation or other type of activity aimed at enhancing a certain effect. The current manuscript comprehensively reviews the state of the art on the interactions between natural compounds and brain receptors. This information is of foremost importance when it is intended to investigate and develop cutting-edge drugs, more effective and with alternative mechanisms of action to the conventional drugs presently used for the treatment of neurodegenerative diseases. Thus, we reviewed the effect of 173 natural products on neurotransmitter receptors, diabetes related receptors, neurotrophic factor related receptors, immune system related receptors, oxidative stress related receptors, transcription factors regulating gene expression related receptors and blood-brain barrier receptors.

Contents

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1. Introduction

Over the years, neurodegenerative diseases – such as Alzheimer's (AD), Parkinson's (PD) and Huntington's (HD) diseases – have been the main focus of the research in neuroscience, so as to recognize the cellular changes and pathophysiological mechanisms involved [1]. This group of diseases is characterized by a gradual motor and sensorial loss, as well as deficits of perceptual functions, knowledge and behaviour associated with neuronal death [2]. This progressive loss of neurons is associated with deposition of proteins in brain leading to changes in its physicochemical properties [3].

AD is related to amyloid-β (or Aβ peptides), which is formed and deposited in the brain due to the disturbance in the metabolism of the amyloid precursor protein (APP) – a glycoprotein that undergoes proteolytic cleavage, through the α- or β-secretases, within the Aβ domain. Firstly, Aβ monomers aggregate into soluble oligomers that then form insoluble oligomers, generating protofibrils and fibrils. Soluble $A\beta_{1\text{-}42}$ oligomers constitute the more toxic form of the peptide [4]. Moreover, there are aggregates of hyperphosphorylated tau-proteins (or τ-proteins) that mediate neuropathological processes associated with dementia [5,6] and there is also a decrease in the acetylcholine (ACh) levels [7]. In the case of PD, intraneuronal inclusions called Lewy bodies are present in the substantia nigra. Lewy bodies are composed of abnormal α-synuclein which is nitrated, phosphorylated, abnormally conformed and aggregated, and presents altered solubility. Besides Lewy bodies, abnormal neurites containing granular material and α-synuclein filaments (Lewy neurites) are also found in the substantia nigra of PD patients [8]. PD is also characterized by the loss of dopaminergic neurons [9]. Finally, in HD, the mutant Huntingtin protein alters neuronal function – being the striatum neurons more susceptible to its toxic effects, which explains the motor symptoms of this pathology [10].

For the cellular communication, it is necessary a set of physical and chemical stimuli that exert their effects on certain proteins, such as biological receptors. The latter regulate a certain physiological function in response to certain molecules [11,12]. In the case of brain receptors, they can be divided into four major types, depending on whether they are ionic channels activated by ligands (ionotropic), G protein-gated ion channels (metabotropic), receptors with enzymatic activity (kinase-linked receptors) or receptors that regulate gene transcription (nuclear receptors) [13,14].

The process of neurodegeneration is related to changes in brain and, thus, brain receptors are important targets in the development of new neuroprotective drugs (Fig. 1). Actually, proteins such as Aβ peptides have the ability to influence the transmission of excitatory neurotransmitters – for example, ACh and glutamate – with concomitant deleterious effects on brain processes, such as learning and memory [15]. Excessive release of calcium ions (Ca^{2+}) – for instance, through glutamate receptors – contributes to mitochondrial dysfunction, activation of proteases and mechanisms of apoptosis, as well as to the accumulation of reactive oxygen species (ROS) and to the release of nitric oxide (•NO) [16]. In turn, γ-aminobutyric (GABA) inhibition, mediated by the type *A* receptor ($GABA_AR$), is a key element that provides the basis for synchronized neuronal activity [17]. In addition, the loss of dopaminergic neurons is a key mechanism for the neurodegeneration since they are involved in functions such as voluntary movement, attention, memory and learning [18]. Furthermore, cannabinoid receptors are also involved in the process, either by a decrease in the expression of cannabinoid type *1* receptors (CB1Rs) – which is associated with an increased release of glutamate, thus contributing to excitotoxicity mechanisms [19] – or by overexpression of cannabinoid type *2* receptors (CB2Rs) – which are involved in processes of neuroinflammation [20,21]. In addition, the activation of receptors of advanced glycation end-products (RAGE) in neuronal cells promotes synaptic dysfunction and, in microglia cells, induces inflammation [6,15]. At the genetic level, peroxisome proliferator-activated receptors (PPARs) play a crucial role in downregulation of mitochondrial dysfunction, oxidative stress and neuroinflammation [22]. Such mechanisms of neuroinflammation involve cells from the immune system (for example, microglia) which, in response to a persistent stimulus (for example, by protein aggregates), activate the production of neurotoxic factors that amplify the inflammatory states. At the same time, the scavenger receptors (SCARs) – highly expressed in astrocytes and microglia – are involved in the capture of several substrates, such as oxidized proteins, lipids and apoptotic cells [23]. Receptors related to neurotrophic factors (NTF) regulate the growth, differentiation and survival of the neurons from the central and peripheral nervous system, and a greater expression of p75 neurotrophin receptors ($p75^{NTR}$) and a lesser expression of tropomyosin/tyrosine receptor kinases (Trk) contributes to the development of neurodegenerative diseases [24]. Moreover, inhibition of insulin/insulin-like growth factor (IGF) signalling contributes to the pathogenesis of AD, as it increases the activity of kinases that catalyses τ-protein hyperphosphorylation and Aβ oligomer accumulation [5]. Finally, in the blood-brain barrier, receptors such as low-density lipoprotein receptor-related protein *1* (LRP1) carry several ligands, such as Aβ and Apolipoprotein E (ApoE)-Aβ complexes (ApoE-Aβ) [25], influencing the supply of cholesterol for neuronal development and maintenance of plasticity and function of neurons [25–27].

Regarding natural products, it is important to underline the enormous diversity of classes of compounds, namely flavonoids, alkaloids, terpenoids and fatty acids, among others, which can bind

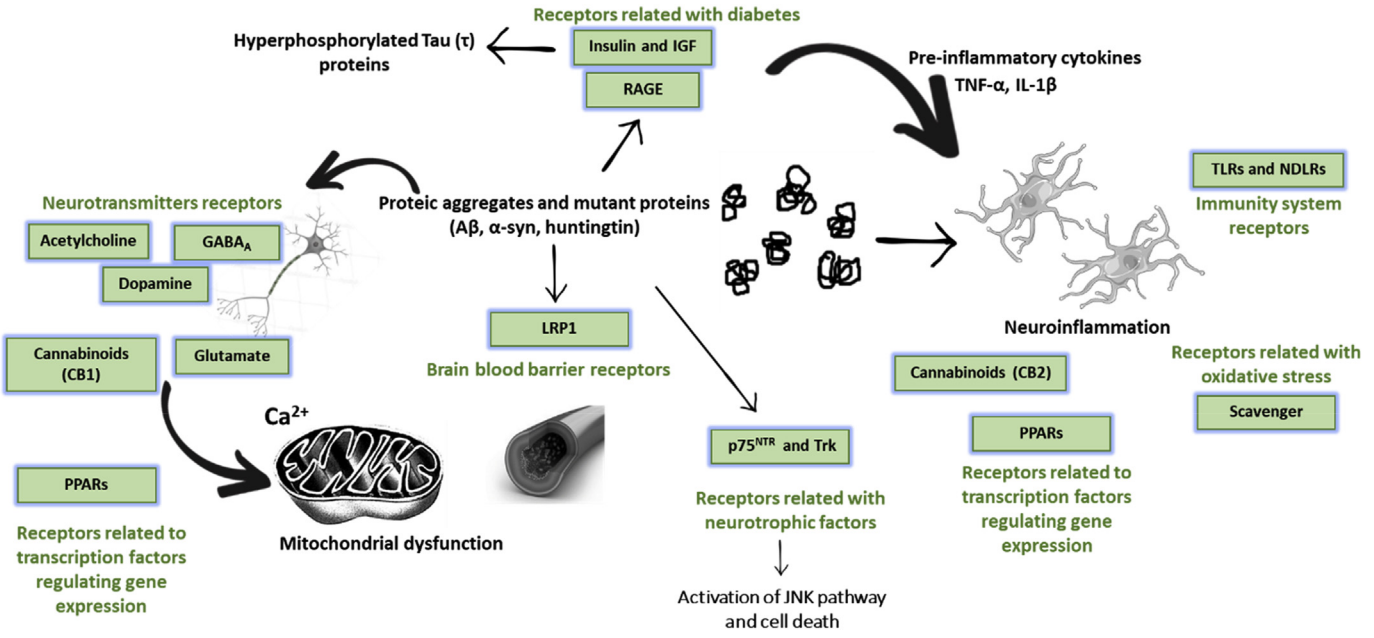

Fig. 1. General view of different types of receptors and their abnormalities in neurogenerative diseases. The brain receptors are important targets for the treatment of neurodegenerative diseases. In fact, aggregates Aβ, α-synuclein and the mutant protein huntingtin can directly modulate the transmission of excitatory neurotransmitters as acetylcholine and glutamate, with disastrous consequences to brain processes, as knowledge and memory. Also, the interaction of the aggregates with dopamine receptors takes to loss of dopaminergic neurons, as well as decrease or up-regulation of GABA receptors, involved in the synchronization of neuronal activity. It is to emphasize that the downregulation of cannabinoids receptors CB1 and the excessive activation of glutamate receptors leads to excessive release of Ca^{2+} and, consequently, to activation of proteases and apoptosis mechanisms, as well as ROS accumulation and •NO release leading, thus, to mitochondrial dysfunction. Besides that, the inhibition of signalization through insulin and IGF receptors, particularly, leads to Tau proteins hyperphosphorylation and the formation of insoluble fibrils toxic for the neurons. The activation of RAGE receptors, which bind the AGEs (protein aggregates) takes, among other processes, to neuroinflammation, through production of pro-inflammatory cytokines. The presence of immune system receptors, as Toll-like receptors and NOD-like receptors, leads to the activation of microglia, through production of TNF-α and IL-1β which promote neuronal death. Also, the upregulation of CB2 receptors, as well as PPARs and scavenger receptors takes to neuroinflammation processes. Blood-brain barrier receptors, as LRP1, make the transport of ApoE and proteins Aβ complexes, influencing the cholesterol supplement to the neurons. Finally, the aggregates lead to a higher expression of $p75^{NTR}$ neurotrophic receptors and a lower expression of Trk, taking to the activation of intracellular signalization pathway JNK, which culminates in cell death.

to receptors and activate them (agonists) or, in opposite, make them to remain in a constitutive state (antagonists). Besides, they may also be partial agonists, *i.e.* activate partially the receptor but not at maximum activity. These compounds may also be inverse agonists, leading the receptor to the inactive form and, thus, producing an opposite effect to an agonist drug [12,28]. Finally, they may also act as allosteric modulators, *i.e.* through their binding to the allosteric centre of the receptor and, consequently, change the receptor structure [28] – thus, affecting the interaction between the receptor and the primary ligand – or interfere with receptor expression (Fig. 2a and b). Indeed, studies addressing the effect of flavonoid supplementation in humans and animal diets have shown improvements in cognition function possibly by protecting vulnerable neurons, enhancing existing neuronal function, stimulating neuronal regeneration and counteracting the oxidative stress [29]. For instance, epidemiological studies have shown the association between tea (*Cammelia sinensis* L.) consumption and the reduced risk of AD [30]. Moreover, alkaloid-containing extracts have been used as therapeutic agents for over 3000 years. Their role in the central nervous system (CNS) is well known, either by the neuroprotective effect that characterize some of them or by the additive effect caused by using so-called recreational drugs [31]. It is also worth to mention the protective role of carotenoids, vitamin E and omega-3 fatty acids against age-related cognitive impairments [32,33].

This review summarizes the effect of 173 natural compounds on brain receptors, focusing on their potential role in the treatment of neurodegenerative diseases. Whenever possible, a discussion on the receptor-natural product binding mode will be introduced, based on studies from molecular docking and molecular dynamic simulations, in order to understand deeply the interactions involved. The structures of all 173 natural compounds are displayed in the supplementary data and were drawn according to Refs. [34–43].

2. Neurotransmitter receptors

2.1. Acetylcholine receptors

Neurotransmitter receptors with affinity to ACh, the ACh receptors (AChRs), can be classified as nicotinic (nAChR) or muscarinic (mAChR) types [15].

2.1.1. Nicotinic acetylcholine receptors (nAChRs)

nAChRs are ionotropic receptors and consist of glycoproteins present in nicotinic cholinergic synapses. In mammals, they are in the muscle junction of the peripheral and CNS. As the term suggests, they have affinity for nicotine, one of its agonists, and are composed by different pentameric combinations with similar α, β, γ, δ and ε subunits, which transport Na^+, K^+ and Ca^{2+} ions through the plasma membrane [44].

nAChRs appear mostly in the form of heteromers with a combination of at least 2 subunits: an α subunit, which has the agonist binding site (positive face); and an accessory unit with β, γ or ε subunits (negative face). However, some receptors may be present in the form of homomers, such as nAChRα7 or nAChRα9, where each subunit has two binding site faces [7,15].

The most expressed nAChR in the mammalian brain is the heteromer α4β2 receptor, which presents two different stoichiometries, $(\alpha4)_3$ $(\beta2)_2$ and $(\alpha4)_2$ $(\beta2)_3$, the former having low

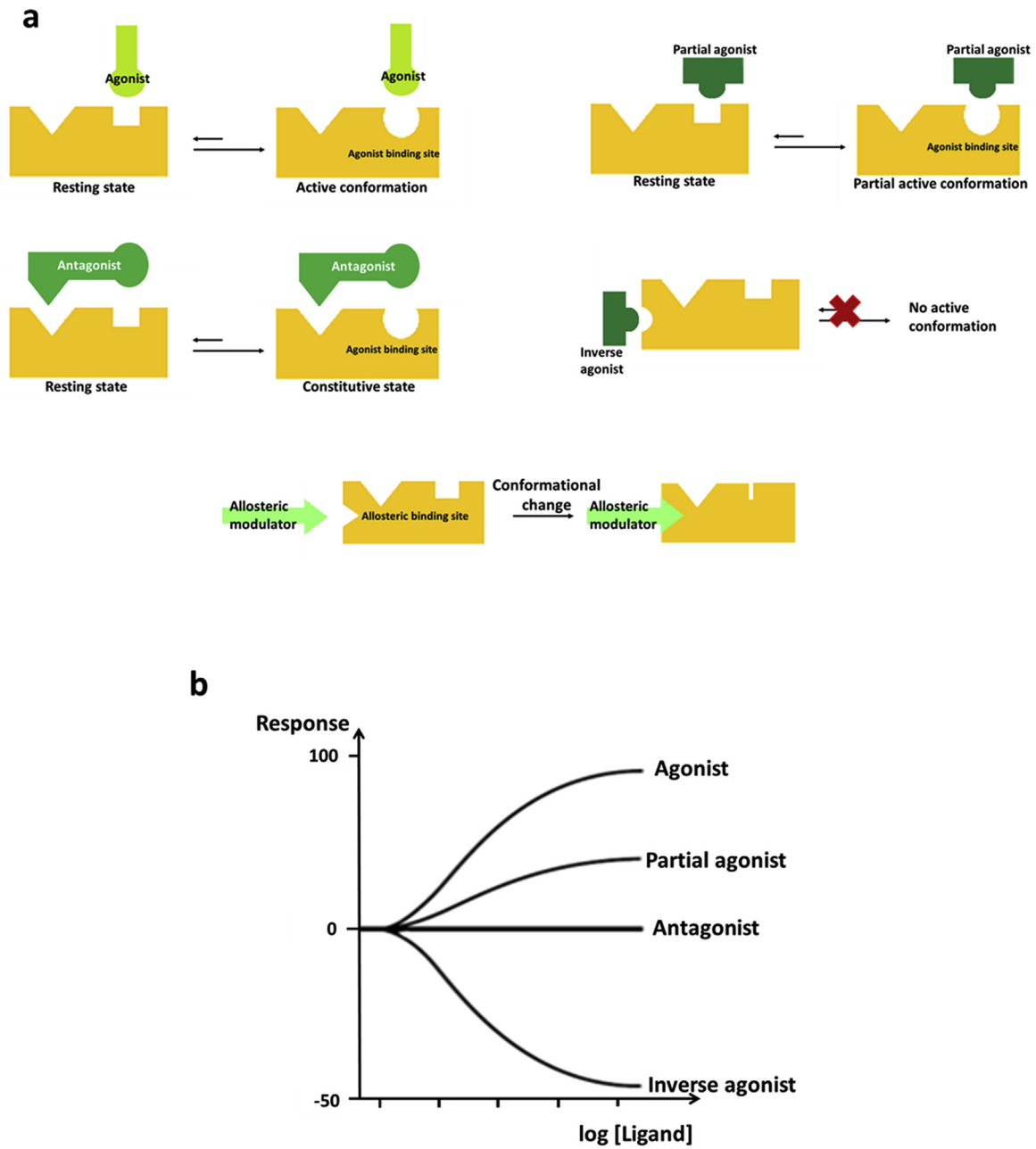

Fig. 2. a) Models of binding mechanisms between ligands and receptors. b) Amplitude of receptor response to different types of ligands.

sensitivity for the agonist, while the second has high sensitivity [7,45]. The homomer nAChR α7 is the second most expressed and has about 20-fold more permeability to Ca^{2+} than the other nAChRs [45]. Its activation leads to an increase in intracellular Ca^{2+}, which in turn activates cell survival pathways involving the protein calmodulin, phosphatidylinositol 3-kinase (PI3K), and phosphorylated protein kinase B (AkT) with subsequent upregulation of *B*-cell lymphoma *2* (Bcl-2), contributing to the synaptic plasticity. In addition, these receptors are present in astrocytes, activating several signal transduction mechanisms that culminate in the modulation of plasticity [45,46].

The subunits of nAChRs vary in length with a highly conserved transmembrane topology, having an amino (NH_2) terminal region forming a broad hydrophilic domain with about 200 amino acids. The α (*i.e.* α1-9) subunits have two cysteine residues, which are essential for ACh binding, whereas the β, γ, ε or δ subunits are absent in such residues. In addition, the nAChRs have three hydrophobic sequences (M1, M2 and M3) with short hydrophilic binding loops and another hydrophilic broad domain, which varies in sequence between the different above said subunits and contains sites for phosphorylation. Finally, they have a fourth hydrophobic sequence (M4) and a short carboxyl terminal tail. Each subunit crosses the membrane four times and the amino (*N*-terminal or NH_2-terminal) and carboxyl (C– or COOH-terminal) termini are oriented towards the synaptic cleft. The cysteine loop is located at the base of the extracellular domains, which is important for the communication between the neurotransmitter binding sites and the ion channel (Fig. 3a) [44,47].

Since the function of α7 and α4β2 nAChRs is critical for knowledge, sensory processing, attention and memory, the dysfunction of

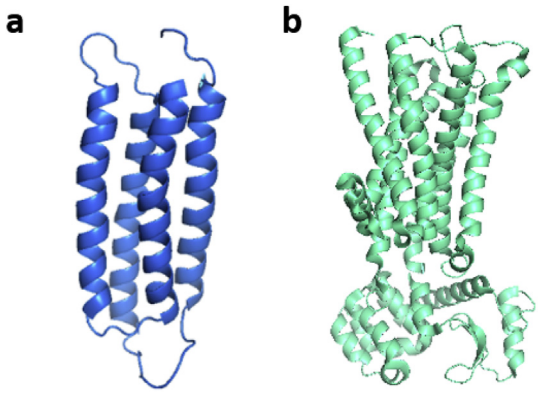

Fig. 3. ACh receptors. a) Image of 2MAW [47] obtained in Pymol. Structure of the α7 nAChR transmembrane domain, from *Homo sapiens*, expressed in *Escherichia coli*. b) Image of 5CXV [63] obtained by Pymol. Structure of the M1 mAChR, from *Homo sapiens*, expressed in *Spodoptera frugiperda*.

these receptors is associated with neurodegenerative diseases. In AD, Aβ peptides may exhibit a high affinity for α7 nAChRs, in the picomolar (pM) order, leading to the formation of complexes that influence neurotransmission and synaptic plasticity [48]. On the other hand, there are studies stating that the modulation of Aβ peptides in these receptors is more complex. In fact, this interaction may involve an antagonism effect and inhibition of pre-synaptic nAChRs, causing changes in pre-synaptic Ca^{2+} levels [15]. However, the activation or antagonism of α7 or α4β2 receptors depends on the microenvironment, as well as the concentration, size and conformation of the Aβ peptides [49]. In the case of PD, nAChRs promote dopamine release, and α4β2 and α6β2 receptors in the striatum are responsible for this function [50]. In studies carried out in brains affected by this pathology – as well as in animal models – a decrease of α4β2 and α6β2 nAChRs as well as slight decrease of nAChR α7 was observed [51]. In order to restore the levels of dopamine/ACh, it is important an activation of the nAChRs receptors. Finally, in HD, early studies did not reveal any relation between the levels of nAChRs and post-mortem human HD brains [52].

Table 1 reports natural products that interact with nAChRs, either by antagonism or agonism, such as alkaloids – (−)-nicotine (**1**, Fig. S1), (−)-cytisine (**2**, Fig. S1), (+)-epibatidine (**3**, Fig. S1), anabaseine (**4**, Fig. S1), (+)-anatoxin-a (**5**, Fig. S1), (−)-galantamine (**6**, Fig. S1), dihydro-β-erythroidine (**7**, Fig. S1), methyllycaconitine (**8**, Fig. S1),(−)-lobeline (**9**, Fig. S1), sophoramine (**10**, Fig. S1), ibogaine (**11**, Fig. S1), pibocin (**14**, Fig. S1), crambescidin 359 (**15**, Fig. S1) and monanchocidin (**16**, Fig. S1) – and sphyngolipids – rhizochalin and its aglycone (**12** and **13**, Fig. S1) [34,50,53–59].

ACh-binding proteins (AChBP) share 20–24% sequence identity with the ligand-binding domain of nAChRs and almost all residues that are conserved within the binding domains of the nAChRs are also present in AChBP. For these reasons, AChBPs have been used as model systems to study ligand-nAChR interactions. AChPBs from freshwater snail *Lymnaea stagnalis* have also high sensitivity for the nAChRs ligands ACh, nicotine (**1**, Fig. S1), cytisine (**2**, Fig. S1), epibatidine (**3**, Fig. S1) or dihydro-β-erythroidine (**7**, Fig. S1). Studies of co-crystal structures of AChBP with these agonists allowed to understand that the interactions involve a binding site composed by the loops A, B and C (at the α subunit, referred as (+) site) and loops D, E and F (at the β subunit, known as (−) side). The binding site is formed by residues of tyrosine, Tyr and tryptophan, Trp from these loops: from loops A (one residue of Tyr), B (one residue of Trp), C (two residues of Tyr) and D (one residue of Trp) [55,60]. The ligand-receptor interaction includes four main binding characteristics: (1) a cation-π interaction within the positively charged amine of the ligands (agonist or non-peptide antagonist) and the tryptophan residue at loop B is formed, stabilizing the compound; (2) a hydrogen bond to the backbone carbonyl of that tryptophan residue is formed, but this interaction is only present for some agonists; (3) also, the ligand forms a hydrogen bond with the hydroxy group of the tyrosine in loop A; and, (4) the two tyrosine residues at loop C establish aromatic and/or hydrogen bonds with the ligand. Residues on the complementary side play a key role in fine-tuning agonist function and subtype selectivity. In addition, agonists and small antagonist interact with the main chain by water-mediated hydrogen bond to a methionine residue at the complementary subunit, and this binding is important as agonist pharmacophore. In summary, while agonist interactions with the principal α-subunit are crucial for binding affinity, interactions with key amino acids present in the complementary β-subunit affect agonist efficacy [55,60].

A plausible molecular mechanism for competitive inhibition of α4β2 nAChRs by *Erythrina* alkaloids (such as dihydro-β-erythroidine (**7**, Fig. S1)) was proposed, in which conserved aromatic residues within loops A and B of the α4 subunit and a moderately conserved aspartate (Asp) residue within β2 subunit were predicted to be involved. The mechanism comprises a hydrogen bond formed between α4Tyr126 (loop A) and the lactone group of **7**, which contributes to sensitivity to inhibition by this antagonist. Moreover, **7** forms weak van der Waals type of contact with the aromatic indole ring of α4Trp182 (loop B) and strong ionic bonds between its ammonium centre and β2Asp196 (β2 subunit). Indeed, β2Asp196 is thought to be the major contributor to the sensitivity of α4β2 nAChRs to inhibition by **7** [61]. In addition, it was found that compound **7** stabilizes the loop C in a different way from other competitive antagonists and it was suggested that this compound prevent receptor activation by stabilizing the desensitized state instead of the non-activated state of nAChRs [60].

Finally, structure-activity studies with cytisine (**2**, Fig. S1) and some analogues revealed that substitutions at C-3, C-4, C-5, C-12 positions or at the piperidine nitrogen alters the affinity and selectivity of the ligands for the α4β2 receptor [55].

2.1.2. *Muscarinic acetylcholine receptors (mAChRs)*

mAChRs belong to the superfamily of G-protein-linked receptors and consist of 5 subtypes (M1 to M5), composed of an α-helix transmembrane domain (TM) (TM I to VII), connected by 3 extracellular and 3 intracellular loops (Fig. 3b) [15,62,63]. The receptors are divided into two distinct classes, according to the signal transduction mechanism [64,65]. mAChRs M1, M3 and M5 are couple with $G_{q/11}$ proteins. They mobilize inositol trisphosphate (InsP3) and diacylglycerols (DAG), increasing the intracellular concentration of Ca^{2+}, and may also activate other intracellular messengers, such as nitric oxide ($^{\bullet}NO$) or phospholipase *A2*, although these effects are secondary to the elevation of intracellular Ca^{2+} concentration [64,65]. In turn, M2 and M4 subtypes affect the signalling through $G_{i/0}$ proteins to inhibit adenyl cyclase (AC) and reduce the intracellular concentration of 3′,5′-cyclic adenosine monophosphate (cAMP) [65].

The M1 receptor is the predominant mAChR in the CNS playing a crucial role in memory and recognition associated with the hippocampus, as well as in the increase of α-secretase activity, preventing the formation of Aβ plaques [15,66]. The use of acetylcholinesterase inhibitors or muscarinic agonists increases receptor activation, thus improving cognitive decline and decreasing Aβ plaque formation [65].

The M2 mAChR subtype is predominantly located in the brainstem and hypothalamus, being related to the control of ACh release. Since selective muscarinic M2 antagonism increases cholinergic

Table 1
Natural products interacting with nAChRs and with mAChRs. Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
(−)-Nicotine (**1**) (*Nicotiana tabacum* L.)	Alkaloid	Agonist of several subtypes of nAChRs; Antagonist of nAChR α9	[50]
(−)-Cytisine (**2**) (*Laburnum anagyroides* Medik.)	Alkaloid	Partial agonist of neuronal nAChRs; Partial agonist of α4β2 nAChRs	[50,53–55]
(+)-Epibatidine (**3**) (skin of poisonous frog *Epipedobates Anthonyi* Noble)	Alkaloid	Agonist of several subtypes of nAChRs; Antagonist of nAChR α9; Decrease of the α4β2 nAChRs activity; High selectivity and toxicity, being required the synthesis of analogues	[50]
Anabaseine (**4**) (certain species of ants, *Aphaenogaster* sp. Mayr, and marine worms, *Nemertines*)	Alkaloid	Powerful agonist of all types of neuronal nAChRs	[50,54]
(+)-Anatoxin-*a* (**5**) (cyanobacteria *Anabaena flos-aquae* Brébisson ex Bornet & Flauhault and *Aphanizomenon flos-aquae* Ralfs ex Bornet & Flahault)	Alkaloid	Irreversible agonist of nAChRs	[56]
(−)-Galantamine (**6**) (*Galanthus nivalis* L.)	Alkaloid	Allosteric potentiation ligand that modulates nAChRs to increase ACh release	[57]
Dihydro-β-erythroidine (**7**) (*Erythrina* spp.)	Alkaloid	Competitive antagonist of α4β2 nAChRs	[55,58]
Methyllycaconitine (**8**) (*Delphinium glaucum* S. Watson)	Diterpenoid alkaloid	Selective nAChR α7 antagonist	[55,59]
(−)-Lobeline (**9**) (*Lobelia inflata* L.)	Alkaloid	Agonist of the nAChRs	[57]
Sophoramine (**10**) (genus *Sophora* L., such as *S. alopecuroides* L.)	Alkaloid	Agonist of the nAChRs	[57]
Ibogaine (**11**) (*Tabernanthe iboga* Baill)	Alkaloid	Blocking of the nAChRs (inhibit nAChRs-mediated catecholamine release)	[57]
Rhizochalin (**12**) and aglycone of rhizochalin (**13**) (sponge *Rhizochalina incrustata* Dendy)	Sphyngolipids	High potency of binding to nAChRs α7	[34]
Pibocin (**14**) (Far-Eastern ascidian *Eudistoma* sp.)	Alkaloid	High potency of binding to nAChRs α7	[34]
Crambescidin 359 (**15**) (Australian sponge *Monanchora clathrata* Carter and sponge *Monanchora unguiculata* Dendy)	Alkaloid	High potency of binding to nAChRs α7	[34]
Monanchocidin (**16**) (sponge *Monanchora pulchra* Lambe)	Alkaloid	High potency of binding to nAChRs α7	[34]
(+)-Muscarine (**17**) (*Amanita muscaria* (L.:Fr.) Lam., a basidiomycete mushroom)	Alkaloid	Agonist of the M1-M5 mAChRs, producing the same effects as ACh	[54]
(+)-Pilocarpine (**18**) (*Pilocarpus* spp.)	Alkaloid	Agonist of the M1-M5 mAChRs	[67]
Cryptolepine (**19**) (*Cryptolepis sanguinolenta* (Lindl.) Schlt)	Alkaloid	Antagonist of the M1, M2 and M3 mAChRs	[67]
(+)-Himbacine (**20**) (*Galbulimima baccata* F. M. Bailey)	Alkaloid	Antagonist of the M2 and M4 mAChRs	[67,68]
Ebeinone (**21**) (*Fritillaria imperialis* L.)	Alkaloid	Antagonist of the M2 mAChRs	[67]
Atropine (**22**) and (−)-Scopolamine (**23**) (*Scopolia tangutica* Maxim.)	Alkaloids	Very powerful antagonist of the M3 mAChRs	[69]
Arecoline (**24**) (*Areca catechu* L.)	Alkaloid	Activation of M2 mAChR, but not of the nAChRs	[57]
Luteolin (**25**) (Compound present in many fruits, vegetables and medicinal herbs)	Flavonoid	Binding activity to M1 mAChRs	[70]
Ombuin (**26**) (*Erythroxylu* spp.)	Flavonoid	Binding activity to M1 mAChRs	[70]
3′,4′,5′,5,6,7-hexamethoxyflavone (**27**) (*Eremophila debilis* (Andrews) Chinnock)	Flavonoid	Binding activity to M1 mAChRs	[70]
Sitoindosides VII-X (**28**–**31**) and withaferin A (**32**) (*Withania somnifera* (L.) Dun.)	Sitoindosides (acylsterylglucosides); Withaferin A (steroidal lactone)	Enhancement of M1 mAChRs binding sites	[57]

overflow by reducing autoreceptor function in both the brain and the periphery, the development of M2 antagonists for the improvement of AD symptoms is necessary. M3 and M5 mAChR subtypes are expressed at much lower levels than M1 and M2 in the CNS – with M3 being found in the cortex and hippocampus, whereas M5 have a discrete localization in the substantia nigra. Finally, M4 mAChR subtype is located in various regions of the brain, predominantly in the striatum, where they possibly play a role in the control of dopamine release and locomotor activity. Research studies have revealed that the use of mAChR M4 receptor antagonists have some usefulness in restoring the dopamine/ACh balance which is imbalanced in PD [65]. Table 1 tabulates natural products that interact with mAChRs, namely the alkaloids (+)-muscarine (**17**, Fig. S1), (+)-pilocarpine (**18**, Fig. S1), cryptolepine (**19**, Fig. S1), (+)-himbacine (**20**, Fig. S1), ebeinone (**21**, Fig. S1), atropine (**22**, Fig. S1), (−)-scopolamine (**23**, Fig. S1) and arecoline

(**24**, Fig. S1); the flavonoids luteolin (**25**, Fig. S1), ombuin (**26**, Figs. S1) and 3',4',5',5,6,7-hexamethoxyflavone (**27**, Fig. S1); and the acylsterylglucosides sitoindosides VII, VIII, IX and X (**28**–**31**, Fig. S1) and the steroidal lactone withaferin A (**32**, Fig. S1) [54,57,67–70].

Molecular modelling studies were carried out in order to understand how luteolin (**25**, Fig. S1), ombuin (**26**, Fig. S1) and 3',4',5',5,6,7-hexamethoxyflavone (**27**, Fig. S1) interact with M1 mAChR. The authors found that these compounds bind to the orthosteric site, mainly through non-polar (van der Waals, π-π and hydrophobic) interactions with several residues such as Tyr106 (TM3), Trp157 (TM4), Trp378 (TM6), Tyr381 (TM6) and Tyr404 (TM7). Structure-activity studies showed that these flavonoids are able to bind key residues through substituents in ring B (Asp105 (TM3), Tyr 404 (TM7), Tyr408 (TM7) and Tyr381), through the carbonyl oxygen of the ketone moiety in ring C (asparagine, Asn382 (TM6) and threonine, Thr192 (TM5)) or C3 at ring C (Trp378) or the substituents at ring A (Trp157) [70].

Pilocarpine (**18**, Fig. S1) forms a polar charged interaction with the conserved Asp105, cation–π interactions with the aromatic residues Tyr106, Trp378, Tyr381, Tyr404 and Tyr408 through their positively-charged head groups, and hydrophobic interactions with other residues, including alanine, Ala196 (TM5), and cysteine, Cys407 (TM7). Moreover, hydrogen bonding between both Thr192 and Asn382 and the carbonyl oxygen atom in pilocarpine tail groups are formed. Indeed, Thr192 and Asn382 binding is an important feature for agonist and antagonist binding, respectively, allowing to distinguish between agonists and antagonists [71].

2.2. Glutamate receptors

Glutamate receptors consist into two classes, namely the ionotropic and the metabotropic receptors [15].

2.2.1. Ionotropic receptors

The ionotropic receptors are divided into three classes, according to their specific agonists and/or permeability to different ions, *viz*. N-Methyl D-aspartate (NMDA), α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate [72].

2.2.1.1. N-methyl D-aspartate receptors (NMDARs). N-Methyl D-aspartate receptors (NMDARs) consist of tetramers, with various subunit configurations in different regions of the brain, being involved in glutamatergic transmission and synaptic plasticity, as well as in memory functions and induction of long-term potentiation (LTP) and long-term depression (LTD) of synapses, depending on the different subunits involved [4,8,15]. In fact, the GluN2B diheteromers, as mentioned after that, are involved in the induction of LTD and GluN2A/B triheteromers are related with LTP [73]. This group of receptors are permeable to the Ca^{2+} and Na^{+} ions [69].

Seven subunits were identified in NMDAR, chiefly one GluN1 subunit (or NR1A-H), four GluN2 subunits (GluN2*A* to *D* or NR2*A* to *D*) and two GluN3 subunits (GluN3*A* and *B* or NR3*A* and *B*) (Fig. 4a) [74]. NMDARs are obligatory heterotetramers mainly composed of two copies each of the GluN1 and GluN2 subunits, which bind glycine and L-glutamate, respectively. However, GluN1/GluN3 and GluN1/GluN2/GluN3 also exist. Glutamate binds to the GluN2 subunit and, for the receptor to be functional, glycine binds simultaneously as a co-agonist in the GluN1 subunit [8,45,72]. Variations in the proportions of the GluN2 subunits modify the affinity of the channels to the glutamate ligands as well as the interactions between the GluN1 subunit and the glycine [75].

It should be noted that the GluN2B subunit of NMDAR has been implicated in the regulation action of Aβ oligomers by increasing the Ca^{2+} concentration in the dendritic spines, which results in a reduction in synaptic density, leading to their dysfunction [15]. Finally, as shown in Table 2 [4,40,52,59–66] amino acids such as NMDA (**33**, Fig. S1), cribronic acid (**44**, Fig. S1) and trans-4-hydroxypipecolic acid sulfate (**45**, Fig. S1) function as agonists of NMDARs, activating the receptors, and consequently, increasing the Ca^{2+} intracellular levels, a crucial process for the learning and production of new memories [4]. On the other hand, NMDAR antagonism was observed with triterpene saponins (20(S)-protopanaxatriol (**34**, Fig. S1), ginsenoside 20(S)–Rh_2 (**35**, Fig. S1) and ginsenoside 20(S)-Rg_3 (**36**, Fig. S1)), phenylpropanoids (α- and β-asarone (**37** and **38**, Fig. S1) and eugenol (**39**, Fig. S1)), flavonoids (isoquiritigenin (**49**, Fig. S1)), curcuminoids (curcumin (**50**, Fig. S1)), mono (isoborneol (**51**, Fig. S1)) and diterpenes (15-methoxy-pinusolidic acid (**41**, Fig. S1)), alkaloids ((−)-huperzine A (**42**, Fig. S1), ibogaine (**11**, Fig. S1), lophocladine A (**46**, Fig. S1), rhynchophylline (**52**, Fig. S1), isorhynchophylline (**53**, Fig. S1) and (−)-kaitocephalin (**59**, Fig. S1)), peptides (conantokins (**47**–**49**, Fig. S1) and histogranin (**57**, Fig. S1)), polypeptides and iridoids (8-O-E-*p*-methoxycinnamoylharpagide (**55**, Fig. S1) and harpagide (**56**, Fig. S1)), having pharmacological activity in the CNS, particularly in neurodegenerative diseases such as AD, where it is underlined an excessive activation of NMDARs [77]. Indeed, the referred compounds, acting by NDMARs antagonism, in general way, inhibit the excitotoxicity mediated by glutamate, thus decreasing the Ca^{2+} intracellular levels, promoting an attenuation of oxidative stress and, consequently, decreasing cells damage [4,78,79].

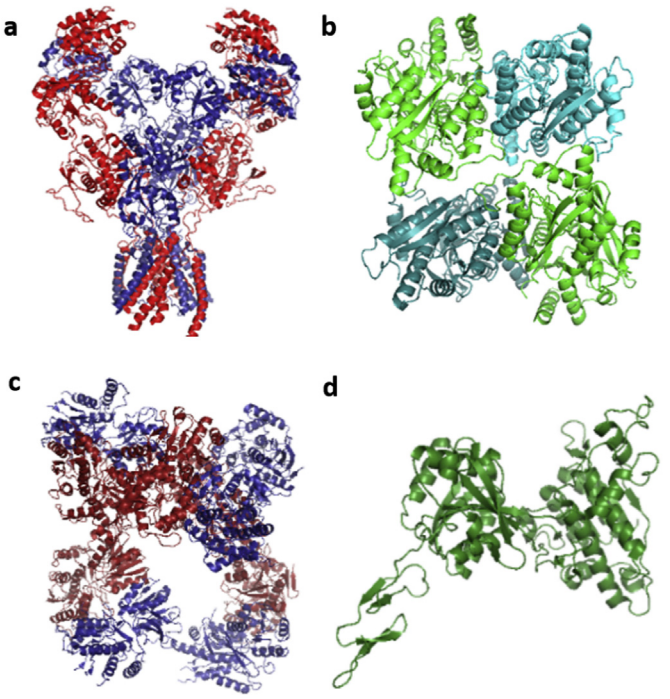

Fig. 4. Glutamate receptors. a) Image of 5FXJ [74] obtained by Pymol. GluN1b-GluN2B NMDAR structure-Class X, from *Rattus norvegicus* expressed in *Homo sapiens*. The red and blue chains represent the subunits NR1B and NR2B, respectively. b) Image of 5FWY [87] obtained by Pymol. Structure of the AMPAR GluA2/A3 N-terminal domain heterodimer, from *Rattus norvegicus* expressed in *Homo sapiens*. The green chains represent the subunits GluA2, while blue chains show the subunits GluA3. c) Image of 3QLV [99] obtained by Pymol. Structure of the GluK2/GluK5 (GluR6/KA2) tetramer assembly of kainate receptors from *Rattus norvegicus* expressed in *Homo sapiens*. The blue chains represent the high affinity subunit GluK5, while the red chains show the low affinity subunits GluK2. d) Image of 5KZN [106] obtained by Pymol. Structure of M2 mGluRs from *Homo sapiens* expressed in *Spodoptera frugiperda*. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Natural products interacting with ionotropic and metabotropic glutamate receptors. Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
N-methyl D-aspartate (NMDA) (**33**) (foot muscle of blood shell *Scaphraca broughtonii* and tunicate *Ciona intestinalis*)	Amino acid	Agonist of the NMDARs	[78]
Ginsenosides (e.g. 20(S)-Protopanaxatriol (**34**); Ginsenoside 20(S)–Rh_2 (**35**); Ginsenoside 20(S)-Rg_3 (**36**)) (*Panax ginseng* C. A. Mey)	Triterpene saponins	Decrease ionic current mediated by NMDARs; Antagonists that selectively inhibit NMDAR through the polyamine binding (ginsenoside 20(s)-Rh_2) or glycine binding (Ginsenoside 20(S)-Rg_3) sites	[4,68,77]
α- and β-Asarone (**37**, **38**) and Eugenol (**39**) (*Acorus gramineus* Sol. Aiton.)	Phenylpropanoids	Neuroprotection against excitotoxicity induced by NMDA or glutamate; Increase cell survival: inhibition of Ca^{2+} influx	[79,80]
Isoliquiritigenin (**49**) (*Glycyrrhiza glabra* L.)	Flavonoid	Binds to the NMDAR, inhibiting the increase of the Ca^{2+} influx into cells induced by glutamate	[4]
15-Methoxy-pinusolidic acid (**41**) (*Platycladus orientalis* (L.) Franco)	Diterpene	Binds to the NMDAR; inhibition of excitotoxicity induced by glutamate, stabilizing Ca^{2+} homeostasis and attenuating oxidative stress	[4]
(−)-Huperzine A (**42**) (*Huperzia serrata* (Thunb.) Trevis.)	Alkaloid	Block of toxicity induced by NMDAR, possibly by binding to the channel pore	[79,80]
Polypeptides (*Achyranthes bidentata* Blume)	Polypeptides	Diminution of NMDA-induced intracellular Ca^{2+}, through modulation of the NR2A and NR2B receptor subunits	[4,80]
Nobiletin (**43**) (*Citrus aurantium* L.)	Flavonoid	Reverses the NMDAR antagonism by activation of ERK signalling; Increases protein Kinase *A* (PKA) activity and phosphorylation of GluA1 (AMPAR), increasing the post-synaptic response to glutamate	[81]
Cribronic acid (**44**) (*Cribrochalina olembda*, a Paluan sponge)	Amino acid	Agonist of the NMDARs	[78]
trans-4-Hydroxypipecolic acid sulfate (**45**) (Micronesian sponges *Axynella carteri* and *Stylotella aurantium*, as well as from the plant *Peltophorum africanum* Sond.)	Amino acid	Agonist of the NMDARs	[78]
Lophocladine A (**46**) (*Lophocladia* sp., a red algae)	Alkaloid	Antagonist of the NMDARs	[78]
Conantokins -G (**47**), -L (**48**), -R, -T (**49**) and -Prl to -Pr3 (*Conus geographus, Conus lynceus, Conus radiatus, Conus tulipa* and *Conus parius*, a genus of fish hunting snails)	Peptides	Selective antagonists of the NMDARs	[78]
Ibogaine (**11**) (*Tabernanthe iboga* Baill)	Alkaloid	Blocking of the NMDARs	[57]
Curcumin (**50**) (*Curcuma longa* L.)	Curcuminoid (diarylheptanoid)	Inhibitory effects against NMDA stimulation, by decreasing of NR1 subunit phosphorylation; Decreases the expression of mGluR5, inhibiting glutamate release and consequent excitotoxicity	[80,82]
Isoberneol (**51**) (*Valeriana officinalis* L.)	monoterpene	Inhibitory effect on NMDARs when present at low concentrations	[83]
Rhynchophylline (**52**) and isorhynchophylline (**53**) (*Uncaria rhynchophyliia* Miq.)	Alkaloids	Inhibition of NMDA-induced current	[80]
Gastrodin (**54**) (*Gastrodia elata* Blume)	Phenolic glycoside	Suppression of glutamate release induced by NMDAR activation	[80]
8-*O*-E-*p*-methoxycinnamoylharpagide (**55**) and harpagide (**56**) (*Scrophularia ningpoensis* Hemsl.)	Iridoids	8-*O*-E-p-Methoxycinnamoylharpagide suppressed NMDA-induced cell death more specifically than harpagide; Harpagide suppressed NMDA- and kainate-induced cell death	[80]
Histogranin (**57**) (bovine adrenal medulla)	Peptides	Antagonist of NMDARs	[76]
trans-Resveratrol (**58**) (grapes, peanuts, blueberries and dark chocolate)	Stilbene	Increases the levels of AMPAR proteins through increasing intracellular Ca^{2+} levels and the consequent activation of AMPK (AMP activated kinase) and through PI3K/Akt signalling pathway; Inhibition of excitotoxicity associated with post-synaptic KARs	[91]
(−)-Kaitocephalin (**59**) (fungi *Eupenicillium shearii* Stolk & Scott)	Alkaloid	A competitive antagonist of AMPARs, which acts on GluA2 and inhibits the mechanisms of excitotoxicity; It has higher affinity for NMDARs than for AMPARs	[92]
Galactose-binding lectin (marine sponge *Cinachyrella* sp.)	Protein	Inhibition of desensitization of AMPARs, acting on the GluA4 subunit	[93]
(±)-Willardiine (**60**) (*Acacia willardiiana* Rose)	Alkaloid	Agonist of AMPARs; has been used as a scaffold to produce antagonists, in order to inhibit excitotoxicity associated with AMPAR and kainate activation (GluK1 subunits)	[94,95]
Kainate or kainic acid (**61**) (seaweeds *Digenea simplex* (Wulfen) C.Agardh, *Alsidium helmithochorton, Caloglossa leprieurii* (Montagne) G.Martens and *Palmaria palmata* (L.) Weber & Mohr)	Amino acid	Partial agonist of AMPARs; Agonist of KARs, binding to the GluK3 subunit with high affinity, but with low strength; Increases the levels of glutamate	[78,96]
α-Allokainic acid (**62**) (seaweed *Digenea simplex* (Wulfen) C.Agardh)	Amino acid	Partial agonist of AMPARs; exhibit higher affinity and potency to KARs than to AMPARs	[78]
Domoic acid (**63**) (red alga *Chondria armata* (Kützing) Okamura)	Amino acid	High-affinity KARs agonist and partial agonist of AMPARs; Indirect activation of mGluRs through the release of endogenous excitatory amino acids	[78,97]
Dysiherbaine (**64**) (marine sponges *Spongionella chondrodes* de Laubenfels and *Lendenfeldia chodrodes*)	Amino acid	Activation of KARs by high affinity binding to the GluK1 and GluK2 subunits but binds to the GluK5 subunit with low affinity; Activation of mGluR5, although with an extremely weak affinity	[78]
Neodysiherbaine A (**65**) (marine sponge *Lendenfeldia chodrodes*)	Amino acid	High-affinity agonist activity on KARs, with a lesser potency for AMPARs	[78]
Galectin CchG (marine sponge *Cinachyrella* sp.)	Protein	Inhibition of desensitization of KARs, acting on the GluK2a subunit	[78]

Table 2 (*continued*)

Compound/Natural source	Compound class	Effect	Refs
Willardiine (**60**) (*Acacia willardiiana* Rose)	Alkaloid	Selective agonist of the KARs that contain the GluK1 subunits	[96]
Caffeine (**66**) (coffee flowering plants)	Xanthine	Acts in post-synaptic sites, blocking the increase of intracellular Ca^{2+} as a result of the activation of mGluRs	[101]

In silico analysis of the binding interaction of conantokins (**47**–**49**, Fig. S1) with the NR2B subunit of human NMDAR was performed and it was found that residues of glutamic acid (Glu236) and glutamine (Gln110) were mainly involved in hydrogen bonding of the NR2B subunit with all conantokins, while hydrophobic interactions were established between residues of isoleucine (Ile110), phenylalanine (Phe114) and proline (Pro177) of NR2B with those antagonists [84].

2.2.1.2. α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). The α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) consist of hetero-tetramers composed by GluA1 to GluA4 subunits (GluR1 to R4) expressed throughout the CNS [72,85,86]. In adult hippocampus, AMPARs are typically composed by GluA1 and GluA2 or, alternatively, by GluA2 and GluA3 subunits (Fig. 4b) [87]. Each subunit contains four distinct domains, *viz.*: an *N*-terminal; a *C*-terminal; a membrane domain consisting of 3 α-helix transmembrane domains (M1, M3 and M4) and a pore channel loop (M2); and a ligand binding domain, composed of S1 and S2 polypeptide sections [86,88,89].

Many of the AMPARs found in the CNS contain GluR2 subunits and are permeable to Na^+ and K^+ ions, but not to Ca^{2+}. Conversely, receptors that do not have GluR2 subunit are permeable to all the three ions [72,85,89]. Particularly, the Ca^{2+} ion-permeable AMPARs are involved in synaptogenesis and neural circuit formation [89].

When glutamate is released from the pre-synaptic terminal nerves, post-synaptic NMDARs and AMPARs mediate the influx of cations, resulting in excitatory impulses (the excitatory post-synaptic current, EPSC) leading to cell depolarization [85]. Excessive activation of AMPARs result in excessive release of Ca^{2+}, leading to mitochondrial dysfunction, activation of proteases and mechanisms of apoptosis, as well as to ROS accumulation and $^{\bullet}NO$ release [16,90]. Accordingly, a strategy to be used to limit the progression of AD could be, for instance, the development of antagonists of Ca^{2+}-permeable AMPARs, at a pre-symptomatic stage of the disease [4,8,86]. In Table 2 it can be seen that *trans*-resveratrol (**58**, Fig. S1) increases the levels of AMPAR proteins leading to the activation of AMP activated kinase (AMPK) and PI3K/atk signalling pathway, while the alkaloids (−)-kaitocephalin (**59**, Fig. S1) and willardiine (**60**, Fig. S1) act as competitive antagonist and agonist of AMPARs, respectively [78,81,91–97].

(−)-Kaitocephalin (**59**, Fig. S1) displays a differential affinity for the different subtypes of ionotropic glutamate receptor which is due to different amino acid compositions of the binding site. (−)-Kaitocephalin contains two moieties that can mimic glutamate and bind to GluA2 subunit of AMPARs. One moiety comprises the C2 nitrogen as the α-amine group of the glutamate and C1 carboxyl group as the α-carboxylate of glutamate; In the other moiety, these functions are displayed by the nitrogen on the pyrrolidine ring and the C18 carboxyl group, respectively. Crystallography studies have shown that: (1) C1 carboxyl group interacts with the side chain guanidinium of an arginine residue (Arg485) and the backbone amide of Thr480; (2) C2 amine interacts with the backbone carbonyl of Pro478, the side chain carboxyl of Glu705, and the side chain hydroxy of Thr480; (3) C18 carboxyl interacts with the amide of Ser 654 and also with the amide and side chain hydroxy of Thr655 through a water molecule; (4) C3 hydroxy forms an hydrogen bond with the side chain hydroxy of Ser654; (5) C17 carboxyl interacts with the backbone amides of Tyr450 and Gly451; and (6) the side chain of Tyr450 forms a hydrophobic surface for the pyrrolidine ring and C2. Compound **59** has higher affinity for NMDARs than AMPARs because of the amino acid residues present in the binding pocket. In GluN1 subunit, Glu657 is replaced by Ile691 and the hydrophobic Ile side chain may provide a hydrophobic surface to interact with the dichlorohydroxybenzoyl group of (−)-kaitocephalin. In a similar way, the substitution of Val484 by Glu522 is also ideal to form H-bonding with the hydroxy of the dichlorohydroxybenzoyl group. On the other hand, the water-mediated H-bond established by Thr655 is prevented by the replacement of Thr655 by Val689 [92].

2.2.1.3. Kainate receptors (KARs). Kainate is a mixed agonist that also activates AMPARs, leading to misinterpretations of the role of KARs in the brain [85,88,98]. KARs consist of tetrameric combinations of subunits GluK1, GluK2, GluK3 (or Glu5-7), GluK4 and GluK5 (or KA 1–2) (Fig. 4c) [99]. They may form homomers or heteromers with low affinity (GluK1-GluK3 subunits), whereas the high affinity GluK4 and GluK5 subunits only participate in association with the remaining subunits, leading to the formation of functional receptors [72,98,100].

In brain, KARs play key roles, such as mediating post-synaptic depolarization and transporting some synaptic current, though only occurs in some synapses. In addition, they modulate the release of neurotransmitters such as GABA and glutamate at different sites. Finally, KARs play a dominant role in the maturation of neuronal circuits during their development. These roles are produced in an unconventional environment, since they imply the activation of a *G* protein, leading to the assumption that KARs would be mostly metabotropic rather than ionotropic receptors. Nevertheless, as revealed by the crystallized structure, KAR has a molecular structure similar to that of other ionotropic glutamate receptors [98]. Besides, these receptors have a high permeability to Na^+ and K^+ [72]. As described in Table 2 some natural products employ their effects on these receptors, either by activation or blocking [60,73,78,79]. As examples of KARs agonists, we can mention the amino acids kainic acid (**61**, Fig. S1), α-allokainic acid (**62**, Fig. S1), domoic acid (**63**, Fig. S1), dysiherbaine (**64**, Fig. S1) and neodysiherbaine A (**65**, Fig. S1), as well as the alkaloid willardiine (**60**, Fig. S1).

X-ray crystal structures have shown that the partial agonists kainate (**61**, Fig. S1) and domoate (**63**, Fig. S1) selected the intermediate and open conformation of GluK2 subunit of KAR, while the full agonist glutamate selected the closed conformation. The full cleft closure of GluK2 in the case of these two partial agonists is preventing by Tyr488 residue [102]. In the ligand-binding pocket, the amino acids Arg523, alanine (Ala518) and Thr690 are predicted to be responsible for establishing H-bonding with the α-carboxyl group of the ligands and Thr690 can also establish indirect interactions through water molecules within the binding pocket that act as surrogate ligands. Moreover, the α-amino group is predicted to interacts with Pro516 and Glu738 residues [102].

Dysiherbaine (**64**, Fig. S1) is the strongest KAR agonist. It has five key binding groups to interact with GluK1 through hydrogen

bonds: (1) The C1 α-carboxylate group establishes H-bonds with the side chain guanidinium group of Arg523, Ser689 and Thr518, and the C2 α-amino group H-bonds to the side chain carboxylate group of Glu738, the side chain hydroxyl of Thr518 and Pro516; (2) in addition, the γ-carboxylate group interact via H-bond with the side chain hydroxyl of Thr690; (3) the C8 aminomethyl group hydrogen bonds to the side chain OH of Ser741 and the side chain carboxylate group of Glu738; (4) The C9 hydroxyl establishes an H-bond with Glu738; and (5) the tetrahydrofuropyran ring hydrophobically packs against the side chains of the residues Tyr489, Glu441 and Pro516 at the D1 face of the binding pocket. The replacement of the C8 aminomethyl group by an OH group (in the case of neodysiherbaine A (**65**, Fig. S1)) greatly reduces the strength of the interactions [103].

(−)-Kaitocephalin (**59**, Fig. S1) is a low affinity KAR antagonist. Two important points of interaction on GluA2 (AMPAR) are different in GluK2 (KAR), which are likely to explain the difference in affinity of (−)-kaitocephalin (**59**, Fig. S1) for KARs in relation to NMDARs and AMPARs. The position corresponding to Ser654 in GluA2 is an alanine in GluK2 (Ala660). This would remove the H-bond with the C-3 hydroxy group of (−)-kaitocephalin. Thr480 in GluA2 is Ala487 in GluK2, which removes the H-bond with the C-2 amine of (−)-kaitocephalin. The loss of two hydrogen bonds could account for the difference in the inhibition of GluK2 relative to AMPAR [92].

2.2.2. Metabotropic glutamate receptors (mGluRs)

Unlike ionotropic receptors, which are found primarily on the post-synaptic membrane and mediate rapid excitatory transmission, metabotropic glutamate receptors (mGluRs) are located in several membrane compartments of neuronal cell and glia in the brain and were classified according to their structure and physiological function in three groups [72,104]. Group 1 mGluRs (mGluR 1 and mGluR 5) are mostly localized in somatodendritic domains of neurons, especially in presynaptic regions, whereas Group 2 mGluRs (mGluR 2 and mGluR 3) are present in the somatodendritic compartment and axonal domains. Group 3 mGluRs (mGluRs 4–8), with the exception of mGluR 6 which is only located in retina, are present predominantly in the presynaptic active zone of axon terminals [72,104]. These receptors have an extracellular ligand recognition domain, seven transmembrane regions connected by 3 extracellular and 4 intracellular loops, and a number of conserved cysteine residues that may be involved in the receptor conformation through the formation of intra- or intermolecular disulphide bonds (Fig. 4d) [104–106].

mGluR 1 and mGluR 5 are coupled to phospholipase C via $G_{q/11}$ proteins, promoting the Ca^{2+} output from intracellular reserves. These receptors are involved in synaptic plasticity, establishing new neural networks that form new memories and assist learning through a process called LTP. Glutamatergic synapses plasticity is extremely sensitive to Aβ aggregates, since they inhibit LTP and induce LTD. Thus, the loss of functional hippocampal synapses along with the inhibition of LTP and increase of LTD may be related to the early learning and memory deficits in AD [72,105,107].

Group 1 of mGluRs stimulates Cβ1 phospholipase and the formation of 1,2-diacylglycerol (1,2-DAG) and inositol 1,4,5-triphosphate (InsP3), with the subsequent release of Ca^{2+} from the intracellular reserves through the activation of the InsP3 receptors. 1,2-DAG remains on the plasma membrane and, together with Ca^{2+}, leads to the activation of protein kinase *C* (PKC) which, in turn, activates several proteins such as phospholipase *D*, phospholipase A2, mitogen-activated protein kinase proteins (MAPKs), as well as several ion channels. Furthermore, activation of PKC through the mGluR5 and mGluR1 receptors also leads to the stimulation of NMDARs [105].

Homer proteins regulate signal transduction, synaptogenesis and receptor trafficking, besides maintaining and regulating extracellular glutamate levels in limbo–corticostriatal brain regions [108]. The interaction of mGluR1/5 with homer proteins leads to the activation of several signalling pathways, including the binding to InsP3 and rianodine receptors, as well as to Shank proteins, which are part of the NMDA receptor complex. Moreover, the resulting dimers can also activate AKt through a mechanism involving pyruvate dehydrogenase 1 (PDK1) and PI3K. The stimulation of group 1 mGluR also leads to extracellular signal-regulated kinase (ErK) activation, which is important for modelling cell growth, differentiation and survival [105].

Groups 2 and 3 mGluRs negatively regulate adenylyl cyclase via $G_{i/0}$ and are mostly localized presynaptically, where they act as autoreceptors to inhibit glutamate or GABA release [72,104]. Even though a scientific consensus has not yet been reached on the role of group 2 mGluRs in the pathogenesis of AD, abnormal expression of these receptors in the hippocampus may be at the basis of Aβ production/release deregulation [105].

Modulation of the mGlu5 and mGlu2/3 receptors represents a key strategy for PD treatment, since the glutamate and dopamine systems exert opposite effects. Since mGlu5 activation indirectly enhances NMDA activity and induces LTD, the use of mGlu5 antagonists reduces the excitatory responses mediated by the activation of mGlu1 and, hence, the release of glutamate. On the other hand, the use of mGlu1 antagonists showed limited beneficial effects. Nevertheless, many effects of the activation of these receptors are changed in animal models with dopamine deficiency, suggesting that mGlu1 and mGlu5 have redundant roles [109]. In opposite to mGluR type 1, the mGluR types 2 and 3 inhibit the release of neurotransmitters. Thus, another possible target would be the inhibition of glutamate release with mGlu2/3 and mGlu7 agonists, since they have anxiolytic properties and increase cognitive functions [110]. Table 2 shows natural compounds interacting with mGluRs, namely, curcumin (**50**, Fig. S1), domoic acid (**63**, Fig. S1), dysiherbaine (**64**, Fig. S1) and caffeine (**66**, Fig. S1) [78,80,82,97,101].

2.3. γ-Aminobutyric acid receptors (GABARs)

GABA released from the presynaptic terminals activates two types of receptors (GAB_AR): the ionotropic GABA type A receptors ($GABA_ARs$); and the metabotropic GABA type B receptors ($GABA_BRs$). $GABA_ARs$ and $GABA_BRs$ are located pre- and post-synaptically. $GABA_AR$ is a heterooligomer (Fig. 5) [111] formed by a diversity of 19 subunits with different isoforms of α, β, γ, ε, π and ρ [112–114]. All subunits contain common elements such as a hydrophilic *N*-terminal domain exposed to the synaptic cleft, 3 highly conserved transmembrane domains (TM) (M1, M2 and M3), a hydrophilic domain of variable size – with sites for phosphorylation, separating the M3 and M4 segments, located in the cytoplasm – and a fourth domain connected to M4 – containing the C-terminal. The M2 segment is aligned with the channel and contains a small number of amino acids within the sequence responsible for anionic/cationic permeability. In turn, the M3/M4 linker consists of the intracellular domain that binds the cytoskeleton [112].

Like nAChRs, GAB_ARs are part of the superfamily of ion channels with cysteine loops. Thus, the α subunits of these receptors have a characteristic cysteine-cysteine pair in the *N* extracellular domain [112].

In adult hippocampus, the activation of $GABA_ARs$, at rest, leads to an influx of chloride ions (Cl^-) through the post-synaptic membrane, resulting in membrane hyperpolarization and a decrease in membrane resistance. Thus, $GABA_AR$-mediated inhibition is a key element that provides the basis for synchronized

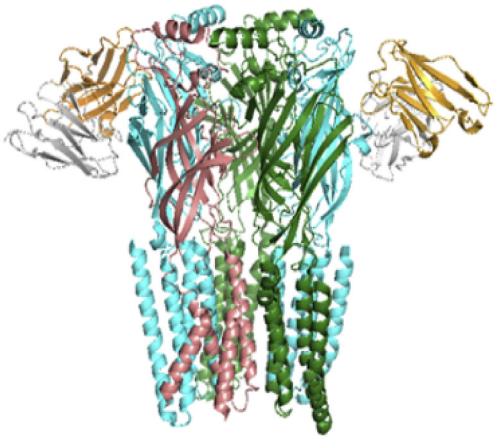

Fig. 5. Image of 6D6T [111], obtained by Pymol. Structure of human $GABA_AR$ α1-β2-γ2 subtype. The green chains represent the subunits β2, the blue cyan ones the subunits α1, while the chain colored by salmon represents the subunit γ2. The grey chains represent the κ Fab light chain and the IgG2b Fab heavy chain is colored by orange. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

neuronal activity and, furthermore, the removal of this inhibition results in epileptiform activity. On other hand, in the immature hippocampus, these receptors have a different role consisting of an excitatory mediation (excitatory postsynaptic potential, EPSP) [17].

Hence, $GABA_AR$ exhibit distinct pharmacological and biophysical properties, including high affinity for their natural GABA ligand, slow desensitization rates and long-lasting activity in the presence of agonists, such as muscimol (**68**, Fig. S1) and valerenic acid (**73**, Fig. S1) (Table 3) [53,57,67,115–118], resulting in low amplitude currents. Additionally, these receptors are located outside the synaptic cleft in the pre- and post-synaptic regions, playing a protective role against excitotoxicity [113]. On the other hand, this effect is counteracted by $GABA_AR$ antagonists, namely the terpenoids bilobalide (**71**, Fig. S1) and picrotoxin (**72**, Fig. S1) (Table 3).

Studies performed on PD mouse models (6-OHDA) revealed a decrease in α1, α2, β2 and γ2 subunits in globus pallidus [119]. In HD, there is over-regulation of the various subunits of $GABA_AR$, as well as of $GABA_BR$ [114]. $GABA_ARs$ are dynamic and circulate constantly between intracellular sites and the plasma membrane, by endocytosis, being susceptible to changes in GABA levels in the cellular environment [120]. This over-regulation may be caused in response to the loss of GABAergic neurons in the striatum of globus pallidus [114].

Muscimol (**68**, Fig. S1) interaction with α1β2γ2 $GABA_AR$ involves residues in α1 and β2 subunits [121]. The positive charge is tucked in between the two C-loop aromatic residues β2Tyr205 and β2Phe200. A salt bridge is formed with β2Glu155 and this residue was identified as a vital residue for $GABA_AR$-ligand binding and channel gating. The acidic moiety of 3-hydroxy-isoxazole of muscimol interacts with α1Arg66 and hydrogen bonds with β2Thr202 and α1Thr129. Finally, a π-cation interaction with β2Phe200 is established. Moreover, the authors argued that a water molecule could mediate further interactions between muscimol and the backbone of β2Ser156 and β2Tyr157 [121].

Fuchs and co-workers evaluated the effect of analogues of magnolol (**69**, Fig. S1) and 4′–*O*-methylhonokiol as positive allosteric modulators of $GABA_ARs$. A magnolol analog with an ethyl and a hexyl residue and a 4′–*O*-methylhonokiol analog with a hexyl residue and a methoxy group were the most potent ones. Smaller or bulky compounds were less potent [118].

2.4. Cannabinoid receptors (CBRs)

The cannabinoid type 1 (CB1R) and type 2 (CB2R) receptors are G-protein coupled receptors that inhibit adenylyl cyclase. It was initially assumed that CB2Rs were found only in cells of the immune system; however, they have now been identified throughout the CNS mainly in microglial cells though at lower levels than those of the CB1Rs [122].

CB1Rs and CB2Rs, as well as the ligands anandamide (N-arachidonoyl ethanolamine, AEA) and 2-arachidonylglycerol (2-AG), and the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) are key elements of the endocannabinoid system, being implicated in physiological functions such as knowledge, motor activity and immune responses [20].

Both the AEA (high affinity, CB1R-selective partial agonist) and the 2-AG (moderate affinity, CB1/CB2 full agonist) are synthesized at post-synaptic terminals from lipid membrane precursors. Both endocannabinoids are not stored in vesicles but are generated on demand and then liberated to act in a retrograde fashion on presynaptically localized CB1Rs [21,123]. Such synthesis occurs in response to high intracellular Ca^{2+} concentrations, by stimulation of mGLuR1, or by entry of Ca^{2+} through the voltage-sensitive channels [21,122,124]. In the cell, AEA is hydrolyzed to arachidonic acid and ethanolamine by FAAH, whereas 2-AG is hydrolyzed by FAAH and MAGL [122].

CB1Rs/CB2Rs (Fig. 6) [125] share 44% homology and are composed by 7 transmembrane domain (TM) coupled to $G_{i/0}$ proteins that perform different pharmacological profiles and expression patterns – a dichotomy that provides a unique opportunity to develop and/or take advantage of pharmacological characteristics [20,126]. Concerning the structure, in the extracellular surface, an extracellular loop and an *N*-terminal region preceding the TM1

Table 3
Natural products interacting with γ-Aminobutyric acid type A receptors ($GABA_ARs$). Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
(S)-Reticuline (**67**) (*Eschscholzia californica* Cham.)	Alkaloid	Positive modulation of α3, α5 and α6 isoforms	[53]
Muscimol (**68**) (*Amanita muscaria* (L.:Fr.) Lam.)	Alkaloid	Agonist of $GABA_ARs$	[67]
Magnolol (**69**) and honokiol (**70**) (*Magnolia* spp.)	Lignans	Positive allosteric modulation of $GABA_ARs$, particularly in the α2 subunit; honokiol has a stronger effect than magnolol	[57,115,118]
Bilobalide (**71**) and picrotoxin (**72**) (*Ginkgo biloba* L.)	Terpenoids	Receptor antagonists, acting on Cl^- channels	[115]
Valerenic acid (**73**) (*Valeriana officinalis* L.)	Terpenoid	Direct partial agonist	[115]
(−)-Epigallocatechin-3-gallate (EGCG) (**74**) (*Camellia sinensis* (L.) Kuntze) and Apigenin (**75**) (present in many fruits and vegetables)	Flavonoids	Increases synaptic inhibition mediated $GABA_A$ (EGCG has a stronger effect); Positive secondary modulation of the benzodiazepine drug effect	[115–117]

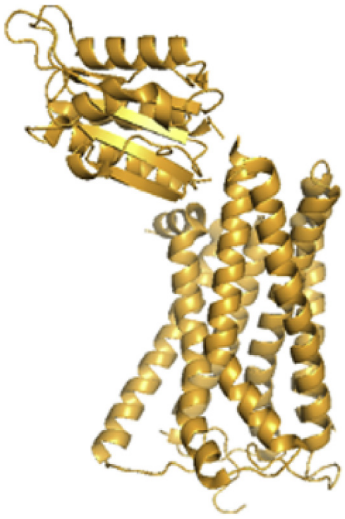

Fig. 6. Image of 5TGZ [125] obtained by Pymol. Structure of the Human CB1R.

domain are found. In addition, a bridge between TM1 and TM7 allows access to lipophilic agonists [126].

CB1Rs are one of the most abundant receptors in the CNS, being implicated in a wide range of brain processes, namely in knowledge and motor coordination. They are located pre-synaptically at the axon terminals of GABAergic neurons [114] and their activation regulates the activity of various plasma membrane proteins and signal transduction pathways. As example, CB1R activation inhibits Ca^{2+} channels, reducing synaptic transmission. It should be noted that, in a mouse microglial cell culture, the activation of the CB1R inhibited the release of $^{\bullet}NO$ – a major component involved in the neurotoxic effects of the Aβ peptides [20].

CB2Rs are primarily expressed in leukocytes and are also present in brain – playing a key role in inflammatory processes. Unlike CB1R, they are highly expressed both in the brains of mice treated with Aβ peptides, as well as in human patients. This overexpression in the microglia cells may be considered an anti-inflammatory response of the CNS in order to protect the neurons from their degeneration. Likewise, it is widely accepted that CB2R activation triggers immunomodulatory effects, resulting in several changes in the production of anti-inflammatory substances, increasing proliferation and recruitment of immune cells into the affected tissue [20,21].

In an early phase of AD and HD, there is a decrease in the expression of CB1R which is associated with an increased release of glutamate, contributing to mechanisms of excitotoxicity. In intermediate and advanced symptomatic phases of HD, there is a significant loss of CB1R – which is compatible with the hyperkinetic symptoms of this disease – whereas in AD there is overexpression of CB1R – which is associated with the akinetic profile of the patients. Finally, the activation of astrocytes and/or microglia in both diseases (AD and HD) is related to over-regulatory responses of CB2Rs and their neuroprotective roles [19].

As showed in Table 4 [19,101,106–126] cannabinoids have antioxidant activity and full and partial receptor agonists – such as Δ9-tetrahydrocannabinol (**76**, Fig. S1), magnolol (**69**, Fig. S1), tetrahydromagnolol (**78**, Fig. S1) and 3,3′-diindolylmethane (**79**, Fig. S1), dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide (**81**, Fig. S1), dodeca-2E,4E-dienoic acid isobutylamide (**82**, Fig. S1) and *trans*-β-caryophyllene (**83**, Fig. S1) – inhibit motor activity, which may be useful for HD, whereas antagonists (e.g. cannabidiol (**77**, Fig. S1), betulinic acid (**92**, Fig. S1), chelerythrine (**94**, Fig. S1), sanguinarine (**95**, Fig. S1), curcumin (**50**, Figs. S1) and 18β-glycyrrhetinic acid (**97**, Fig. S1)) produce opposing effects – which is a useful feature for PD [19].

The interaction of alkylamides with the CB2R was explored by Raduner et al. [146]. A putative binding site for CB2R ligands is located adjacent to helices III, V, VI, and VII at the near extracellular side of the 7TM bundles. The hydrophilic centre is framed by polar residues (Gln276, Tyr190, and Asp189), and a hydrophobic cleft is surrounded by aromatic residues (Phe197, Phe117, and Trp258). Several authors suggested the amino acid residues important for CB2R ligand activity, which comprise the residues Asp130, Arg131, Tyr132, Cys174, and Cys175, which are important for the conformation of the wild-type CB2R; the residues Ser161 and Ser165, which are essential for binding of an antagonist (SR144528); and the residues Tyr190 and Phe197 needed for the binding of agonists [147–152]. Similar to the putative cavity of the CB2R model, the n-alkylamides dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide (**81**, Fig. S1) and dodeca-2E,4E-dienoic acid isobutylamide (**82**, Fig. S1) are also amphipathic molecules with hydrophilic amide and hydrophobic alkyl groups, and their flexible molecular features allowed them to be docked well into the predicted binding pocket. The computer modelling indicated that the amide group of dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide (**81**, Fig. S1) is headed into the hydrophilic pocket, bounded by the residues Asp189 and Tyr190 of the CB2R. Tyr190 not only exhibits an H-bond interaction with the amide hydrogen of the alkylamide but also the aromatic ring of Tyr190 exhibits π-π interactions with the C2–C3 double bond in the alkylamide [146].

Sabatucci et al. [153] performed an *in silico* docking study to find putative allosteric sites for different allosteric modulators of the receptor, and to define their binding affinities. Cannabidiol (**77**, Fig. S1) binds to the orthosteric site and to the allosteric pockets 1 and 3. On the other hand, the agonist Δ9-tetrahydrocannabinol (**76**, Fig. S1) only binds to the orthosteric site. Pocket 1 was identified in the transmembrane region between TM2 and TM4, and ligand binding engaged three amino acids: the conserved residue Trp241 (TM4), the hydrophobic residue Phe237 (TM4), and the positive residue His154 (TM2). Pocket 3 was found in the N-terminal region of CB1R, partially overlapping on the orthosteric site and comprises the residue Cys107; however, interactions in this region were not completely characterized.

2.5. Dopamine receptors (DARs)

Dopamine or 3-hydroxytyramine is a catecholaminergic neurotransmitter which generally exerts its actions on the neuronal circuit through a relatively slow modulation of rapid neurotransmission mediated by glutamate and GABA. Dopaminergic innervations are the most abundant in the brain, being involved in various CNS functions, including the voluntary movement, attention, memory and learning [18].

The physiological actions of dopamine are mediated by five distinct but similar dopamine receptors (DARs) that are coupled to G proteins – whose topology includes seven hydrophobic transmembrane domains (Fig. 7) [154]. All members possess TM amino acid sequence homology and post-translational modifications (such as glycosylation and phosphorylation), as well as preserved amino acid residues involved in interaction with G protein and in binding agonists [155].

The dopamine receptors are grouped into two major groups (1 and 2), according to their ability to modulate the capacity to produce cAMP and according to their distinctive pharmacological properties [18,156–158]. Class 1 DARs include D1 and D5 receptors, which activate the protein family $G_{\alpha s/olf}$ to stimulate cAMP production and are localized exclusively in pre-synaptic neurons. On other hand, D2, D3 and D4 receptors are coupled in class 2, localized

Table 4
Natural products interacting with cannabinoid type 1 (CB1R) and type 2 (CB2R) receptors. Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
Δ9-tetrahydrocannabinol (**76**) (*Cannabis sativa* L.)	Terpenoid	Partial agonist of CB1Rs and CB2Rs; ROS scavengers; direct increase of the activity of endogenous antioxidant enzymes through the modulation of the signalling triggered by the activation of nuclear factor erythroid 2–related factor 2 (Nrf2) (indirect effect from the receptors)	[19,122,140,141]
Cannabidiol (**77**) (*Cannabis sativa* L.)	Terpenoid	High potency antagonist of CB1Rs and CB2Rs; Direct increase of the activity of endogenous antioxidant enzymes through the modulation of the signalling triggered by the activation of Nrf-2 (indirect effect from the receptors)	[19,122,144]
Magnolol (**69**) and tetrahydromagnolol (**78**) (*Magnolia officinalis* Rehder&Wilson.)	Lignans	Activation of the cannabinoid's receptors	[142]
3,3′-diindolylmethane (**79**) (*Brassica* spp.)	Alkaloid	Partial agonist at CB2Rs	[143]
(R)-(−)-Falcarinol (**80**) (species from Apiaceae family, such as *Daucus carota* L.)	Polyacetylene	Inverse agonist of CB1Rs	[143]
Dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide (**81**) and Dodeca-2E,4E-dienoic acid isobutylamide (**82**) (*Echinaceae purpurea* (L.) Moench)	N-alkylamides	Agonist of CB1Rs and CB2Rs (high affinity to CB2Rs); Inhibition of AEA transport; sharing similarities with 2-AG; partial FAAH inhibition; anti-inflammatory proprieties as TNF-α mRNA expression but inhibition of LPS-stimulated TNF- α protein expression (indirect effect from the receptors)	[127,145]
Trans-β-Caryophyllene (**83**) (Found in essential oils of plants such as *Origanum vulgare* L., *Cinnamomum* sp., *Piper nigrum* L., *Rosmarinus officinalis* L.)	Sesquiterpene	Selective full agonist of CB2Rs	[127,128,143]
Dodeca-2E,4E-dienoic acid isobutylamide (**82**), tetradeca-2E,4Edienoic acid isobutylamide (**84**), tetradeca-2E,4E,8Z-trienoic acid isobutylamide (**85**) and 1-[(2E,4E,8Z)-tetradecatrienoyl] piperidine (**86**) (*Otanthus maritumus* L.)	Fatty acid derivates	High binding affinity to CB2Rs	[127]
α and β-Amyrin (**87,88**) (*Protium kleinii* Cuatrec. and *Protium heptaphlyllum* (Aubl.) Marchand.)	Triterpenoid	The 1:1 mixture of both isomers binds to CB1Rs with high affinity and to CB2Rs with lower affinity	[127,129]
Cyanidin (**89**) and delphinidin (**90**) (colored fruits and vegetables)	Flavonoids	Moderate affinity for human CB1Rs	[127,130]
Auroglaucin (**91**) (fungus *Eurotium repens* de Bary)	Alkaloid	Binding affinity to CB1Rs and CB2Rs	[127]
Betulinic acid (**92**) (*Betula pubescens* Ehrh.)	Triterpenoid	Antagonist of CB1Rs and agonist of CB2Rs	[127,139]
Celastrol (**93**) (*Tripterygium wilfordii* Hook.f. and *Celastrus scandens* Lime)	Triterpenoid	Agonist of CB2Rs	[127,131]
Chelerythrine (**94**) (*Chelidonium majus* L.)	Alkaloid	Antagonist of CB1Rs	[127,132]
Sanguinarine (**95**) (poppy seeds, such as *Papaver somniferum* L.)	Alkaloid	Antagonist of CB1Rs	[132]
Curcumin (**50**) (*Curcuma longa* L.)	Curcuminoid (diarylheptanoid)	Antagonist of CB1Rs	[127,133]
Euphol (**96**) (*Euphorbia tirucalli* L.)	Triterpene alcohol	Agonist of CB1Rs and CB2Rs	[127]
18-Glycyrrhetinic acid (**97**) (*Glycyrrhiza glabra* L.)	Triterpenoid saponin	Antagonist of CB1Rs	[127,134]
Salvinorin A (**98**) (*Salvia divinorum* Epling & Játiva)	Diterpenoid	Agonist of CB1Rs	[127,135–137]
Malyngamide B (**99**) (marine cyanobacteria *Lyngbya* spp.)	Fatty acid amide	Agonist of CB1Rs and CB2Rs	[35,127]
Rutin (**100**) (Citrus species, *such as Citrus sinensis* (L.) Osbeck)	Flavonoid	Upregulation of CB1Rs expression	[127,138]
Serinolamide B (**101**) (*Lyngbya* spp., a marine cyanobacterium)	Fatty acid amide	Moderate affinity and higher selectivity for CB2Rs than for CB1Rs	[35,127]

in pre and post-synaptic neurons. These receptors activate the $G\alpha_{i/o}$ proteins, inhibiting the adenylyl cyclase [159].

Class 1 receptors increase the current of the L-type Ca^{2+} channels and decrease those of N-type and P-type. Furthermore, D1 can also mobilize intracellular Ca^{2+} stores by activating the cAMP pathway without activating the phosphoinositide (PI) hydrolysis [159].

Since dopamine is involved in a variety of critical functions, it is easy to relate dopaminergic dysfunctions to neurodegenerative disorders – the most notorious being PD [18]. The classic treatment of this disease involves L-DOPA. Despite time and frequency adjustments of the drug dose, motor fluctuation and involuntary movements (dyskinesia) tend to appear in long-term patients [155]. Generally, agonists increase dopamine function – thus increasing motor activity – whereas antagonists have an opposite effect [159]. The alkaloids (−)-stepholidine (**103**, Fig. S1), (−)-apomorphine (**106**, Fig. S1), (−)-salsolinol (**107**, Fig. S1), ibogaine (**11**, Fig. S1) and ephedrine (**108**, Fig. S1) are among the natural products acting as DAR agonists (Table 5), whereas (−)-epigalhocatechin-3-gallate (**74**, Fig. S1) acts as DAR antagonist (Table 5) [57,160–163]. Since dopamine receptors belong to aminergic G-coupled receptors family, the extracellular loops 1 and 3

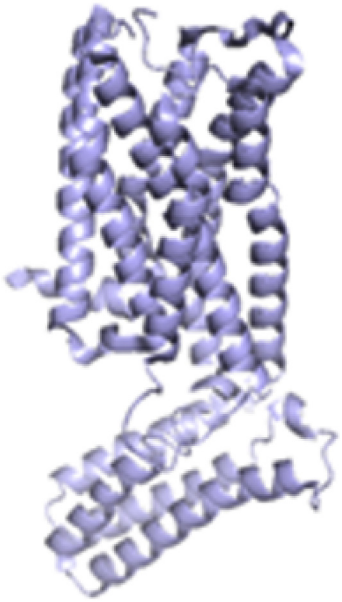

Fig. 7. Image of 5WIV [154], obtained by Pymol. Structure of the human D4 dopamine receptor.

are typically short, while 2 is significantly longer, probably reaching the active site and forming a lid over the bound ligand. In docking studies performed with the compound (−)-stepholidine (**103**, Fig. S1), it was confirmed that the positively charged side chain of Lys167 forms H-bonds with the negatively charged chain of Glu302. Then, this bond is broken and Lys167 gradually approaches Asp173 of the extracellular loop 2, forming indirect H-bonds. In D1 receptors, the distances between the key residues in the active sites fluctuate a little bit and, so the compound acts as agonist. On the other side, in the (−)-stepholidine/D2 complex, hydrophobic interactions between some groups of the receptor and A and D rings of the (−)-stepholidine occur, thus contributing for a perpendicularity between the rings, as contrary to (−)-stepholidine/D1 complex, and so contributes for the antagonism to D2 receptors [161].

Also, docking studies performed with apomorphine (**106**, Fig. S1) revealed that, like dopamine, it establishes strong hydrogen bonds with the residues Asp114 (TM3), Ser193 (TM5) and His393 (TM6) of D2 receptor. The H-bond formed with Asp114 is considered a salt bridge between a charged oxygen atom from Asp114 and the protonated nitrogen atom of the ligand. Besides that, His393 residue contributes for a π-π stacking interaction, thus pitch in the activation of the receptors [164].

3. Diabetes related receptors

3.1. Insulin and insulin-like growth factor (IGF) receptors (IR and IGFR)

The insulin receptor (IR) has two isoforms (A and B) that differ slightly in affinity for insulin. The B isoform binds the IGFs with at least 100 times lower affinity than insulin, while the A isoform has significantly higher affinity than the B isoform for IGF-I and especially IGF-II. The IGF-I receptor binds IGF-II with a lower affinity than IGF-I and insulin with a 500-fold lower affinity [165]. The insulin and the IGF receptors are heterotetramers assembled from α and β subunits (α2β2). The α-subunit has a cysteine-rich domain and a carboxy-terminal (αCT) and contains the site or sites for ligand binding, whereas the β-subunit is composed by three regions, namely, extracellular, transmembrane and cytosolic domain. The extracellular portion of each αβ protomer contains six domains (L1, CR, L2, FnIII-1, FnIII-2 and FnIII-3) and an insert domain within FnIII-2. α- and β-subunits are linked by disulfide bonds. The greatest similarity between both receptors is found in the tyrosine kinase domain located in the cytosolic region of the β-subunit where the homology is 84% [166–168].

This group of receptors are present in the CNS, being expressed in neurons and glia cells [169]. When ligands bind, subsequent phosphorylation (activation) of the intrinsic receptor tyrosine kinase (RTK) occurs, promoting signal transduction mechanisms [5,169]. Signalling of insulin and IGF (Fig. 8a) [170] regulates the use of glucose and adenosine triphosphate (ATP) production in brain and is associated with inhibition of apoptosis and regulation of neuronal plasticity as well as with cholinergic functions – which are necessary for learning, memory and maintenance of myelin [169].

Insulin resistance is defined as the state in which elevated levels of circulating insulin (hyperinsulinemia) are associated with hyperglycaemia. As a result, higher levels of ligand are required to trigger normal actions of insulin which leads to a set of events that culminate in negative effects on cells [169].

During caloric restriction, an increase in insulin sensitivity occurs and several signal transduction mechanisms are activated – to potentiate neuroprotective effects. In particular, the binding of insulin and IGF-I molecules to their receptors leads to the activation

Table 5
Natural products interacting with dopamine receptors (DAR). Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
Docosahexaenoic acid (**102**) (Compound extracted from algae and fatty fish)	Fatty acid ω-3	Decreased brain docosahexaenoic acid produced a decreased density of ventral striatal D (2)-like receptors	[163]
(−)-Epigallocatechin-3 gallate (**74**) (*Camellia sinensis* L.)	Flavonoid	Antagonist of DARs	[180]
(−)–Stepholidine (**103**) (*Stephania tetrandra* S. Moore)	Alkaloid	Agonist of dopamine receptor D1 and antagonist of receptor D2	[161]
L-DOPA (**104**) (species of bean as *Mucuna* spp.)	Amino acid	Precursor of dopamine which cannot itself cross the blood-brain barrier	[57]
Ergotamine (**105**) (fungus *Claviceps purpurea* Tulasnae)	Alkaloid	Natural precursor for semi-synthetic drugs as bromocriptine, cabergoline and lisuride (D2Rs agonists) and perfolide (D1, D2 and D3 receptors agonist)	[57]
(−)-Apomorphine (**106**) (*Papaver somniferum* L.)	Alkaloid	Agonist of D1 and D2 receptors	[57]
(−)-Salsolinol (**107**) (*Theobroma cacao* L.)	Alkaloid	Dopaminergic activity in D2 receptors	[57,162]
Ibogaine (**11**) (*Tabernanthe iboga* Baill)	Alkaloid	Enhancement of release of dopamine; poor affinity for dopamine D1Rs and D2Rs	[57,160]
Ephedrine (**108**) (*Ephedra sinica* Stapf)	Alkaloid	Stimulating dopamine D2 autoreceptors	[272]

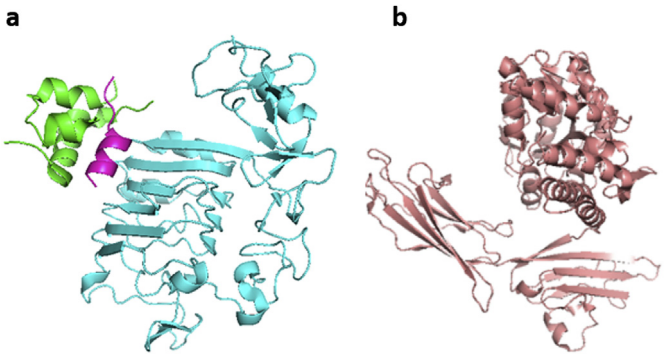

Fig. 8. Diabetes related receptors. a) Image of 4XSS [170] obtained by Pymol. IGF1 in complex with site 1 of a hybrid insulin receptor/Type 1 IGF receptor, from *Homo sapiens*, expressed in *Escherichia coli* and *Cricetulus griseus*. b) Image of 3O3U [274] obtained by Pymol. Structure of human RAGE expressed in *Escherichia coli*.

of the PI3K/Akt cell survival pathway that activates the nuclear transcription factor κB (NF-κB) [171]. In turn, NF-κB increases gene expression, namely the genes involved in the neuronal response (cyclooxygenase, COX, and nitric oxide synthase, NOS) [172]. Furthermore, this signalling cascade also results in the inhibition of the transcriptional activity of Forkhead box *O* (FoxO), involved in neurodegenerative diseases [173].

Thus, inhibition of insulin or IGF actions reduces neuronal survival, and cell death is triggered by apoptosis, neuronal dysfunction or activation of death-signalling cascades, as well as by activation of kinases that phosphorylate tau proteins (τ proteins) and other proteins of the cytoskeleton. Besides, it also promotes oxidative stress that contributes to the neurodegenerative cascade and, ultimately, leads to behaviours associated with dementia and cognitive deficits [174].

In AD, deficits in brain insulin levels and IGF signalling increase throughout pathology progression, along with the decreased brain energy production, gene expression, and plasticity [169]. These abnormalities are associated with low levels of insulin receptor substrate (IRS) mRNA, τ mRNA, IRS-associated PI3K and phospho-Akt (activated), and with increased GSK-3β activity and APP mRNA expression [175]. Thus, AD is associated with insulin resistance and deficiency, and is even called type 3 diabetes [175,176]. As showed in Table 6 a set of natural products, which includes vitamin E (**109**, Fig. S1), *trans*-resveratrol (**58**, Fig. S1), (−)-epigallocatechin-3-gallate (**74**, Fig. S1), theaflavin derivatives (**110**–**112**, Fig. S1) and chaetochromin A (**113**, Fig. S1), may bring beneficial biological effects towards relieving symptoms [5,173,177–179].

In silico docking analysis suggested that chaetochromin A (**113**, Fig. S1) activates IR by binding to the extracellular domain. It binds to the hinge region between the cysteine-rich region and L2 domain. The amino acid residues of the receptor involved in the interaction of chaetochromin A with IR were found to be Glu287, Cys288, Thr293, Cys306 and Lys310. Conversely, insulin B-helix engages the residue Phe39 of the β2-strands at the L1 region and both insulin chains interact with the carboxy-terminal α-chain region, being His710, Asn711 and Phe714 residues the most critical ones. Therefore, chaetochromin A does not bind to insulin binding site [168,179].

3.2. Receptors for advanced glycation end-product (RAGE)

The receptor for advanced glycation end-products (RAGE) is a member of the immunoglobulin superfamily of cell-surface molecules, being unclassified scavenger receptors that act as receptors of various ligands, namely advanced glycation end-products (AGEs), S100 calcium-binding protein *B* (S100B), high mobility group box *1* protein (HMGB-1), and Aβ peptides. Regarding their structure (Fig. 8b) [180], they are constituted by extracellular, transmembrane and cytoplasmic domains. Concerning the extracellular domain, RAGE have a variable domain (V), involved in the recognition of ligands, and two constant domains (C1 and C2) [6,15,181–184].

RAGE are highly expressed in neurons, microglia, astrocytes and endothelial cells. Activation of RAGE in neuronal cells promotes synaptic dysfunction and, in microglia cells, induces inflammation [6,15]. AGEs result from the nonenzymatic reaction of reducing sugars (*e.g.* glucose) with proteins, lipids, and nucleic acids, and they accumulate during aging process [185]. The production of AGEs is increased during hyperglycaemia (diabetes *mellitus*) and other serious pathological conditions, such as AD. In AD, toxic products can be formed due to the inhibition of mitochondrial respiration caused by an abnormal glucose metabolism. Moreover, an increase in unchelated transition metals such as copper (Cu) and iron (Fe) bound to Aβ plaques causes, not only an acceleration of the oxidation of glycated proteins and subsequent increase in highly reactive glycoxidation products, but also promote the aggregation of Aβ peptides. AGEs were also observed to crosslink neurofibrillary tangles [4,186].

The interaction between RAGE and their ligands leads to a rapid production of ROS and pro-inflammatory cytokines through mechanisms of signal transduction and activation of transcription factors – the main signalling pathways activated being Janus kinase (JAK)/signal transducers and activators of transcription (STAT) cascade, GTPases Ras-Rac-cell division control protein 42 homolog (Ras-Rac-Cdc42), PI3K/Akt, MAPK, extracellular signal-regulated kinase 1/2(ErK1/2), stress-activated protein kinase (SAPK)/*c*-Jun NH_2-terminal kinases (JNK) and mitogen-activated protein (MAP) [181].

Table 6
Natural products that act on insulin receptors and insulin-like growth factor receptors (IGFRs). Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
Vitamin *E* (**109**) (Compound present in vegetable oils, nuts, whole grains and green leafy vegetables)	Tocopherol	Increases insulin signalling and glucose utilization in the brain, decreasing the oxidative stress and improving energy metabolism	[177]
trans-Resveratrol (**58**) (grapes, peanuts, blueberries and dark chocolate)	Stilbene	Activation of Sirtuin 1 (SIRT1) triggering a similar effect to caloric restriction: increases insulin sensitivity and activation of Forkhead box O3a (FoxO3a), a key regulator of insulin and IGF-1 signalling	[5]
(−)-Epigallocatechin-3-gallate (EGCG) (**74**) (*Cammelia sinensis* (L.) Kuntze)	Flavonoid	Mimics the cellular effects of insulin, reducing gluconeogenesis and gene expression	[5,178]
Theaflavin 3-*O*-gallate (**110**), theaflavin-3′–*O*-gallate (**111**) and theaflavin 3, 3′-di-*O*-gallate (**112**) (*Camellia sinensis* (L.) Kuntze)	Flavonoids	Mimics the Forkhead box O1a (FoxO1a)	[173]
Chaetochromin A (**113**) (fungus *Chaetomium gracile* Udagawa)	Bis(naphtho-γ-pyrone)	Mimesis of insulin functions to activate the insulin receptor and its downstream signalling pathways *in vitro* and *in vivo*	[179]

In AD, RAGE are responsible for the transport of Aβ peptides from the blood to the brain by transcytosis, inducing cerebrovascular dysfunction – which, in turn, induces in neurovascular inflammation and consequent synaptotoxicity. Furthermore, RAGE amplifies the effects of Aβ peptides in the early stages of the disease, when the level of Aβ is low [4,6,19].

In PD, a robust expression of the receptors in the substantia nigra and in the frontal cortex are observed. Increased binding of AGEs to the RAGE induces and worsens oxidative stress and inflammation – ultimately leading to mitochondrial dysfunction and cell death of neurons. AGE-albumin, the most abundant form of AGE in brain, is synthesized in activated microglial cells and highly expressed in the nervous system of animal models and in humans with this disease. In dopaminergic neurons, the expression of RAGE through these ligands leads to apoptosis of these cells via the MAPK pathway [181].

Finally, an overexpression of RAGE in the neurons from the striatum was observed using an animal model of HD [181]. Indeed, possible causes for elevated RAGE levels were discussed and one hypothesis raised consisted of the mutated huntingtin protein being released from the intracellular space into the extracellular space and subsequently binding to RAGE - triggering a toxic cascade of cytokines and consequently leading to neuronal death [187,188]. However, researchers found out that huntingtin aggregates did not bind to RAGE and that the toxic mechanisms of this protein did not account for all neuronal death associated with the disease, revealing that other mechanisms were also implicated [185]. In Table 7 are presented examples of natural compounds which act on RAGE, in order to reduce the negative effects resulting from their activation [189–193]. This is the case of *trans*-resveratrol (**58**, Fig. S1) and glycyrrhizic acid (**123**, Fig. S1) which reduce RAGE expression, thus ameliorating the disease-associated symptoms.

4. Neurotrophic factor (NTF) related receptors (NTFRs)

The family of neurotrophic factors (NTFs) which includes nerve growth factor (NGF), BDNF, neurotrophin (NT)-4/5 (NT-4/5) and neurotrophin-3 (NT-3) proteins, regulates the growth, differentiation and survival of CNS and peripheral neurons. All proteins are initially produced by a pro-NTFs precursor, and are subsequently processed, by proteolytic cleavage, to mature NTFs that are released to various cell types, including neurons and glia cells. It is noteworthy that pro-NTFs have different binding properties and different functions relative to mature NTFs [24,194]. NTFs act through two distinct receptors: a high-affinity and selective receptor tyrosine kinase called Trk (Fig. 9a) [195] and a low affinity receptor called p75 [24,194].

Mature NTFs bind primarily to one of three Trk isoforms – with NGF preferentially binding to TRkA, BDNF and NT-4/5 to TrkB, and NT-3 mainly to TrkC but also to TrkA and TrkB. These NTFs have a central region that binds to the receptor and three β-loops (loops 1, 2 and 4), inducing the formation of Trk dimers and triggering autophosphorylation into multiple tyrosine residues of the Trk cytoplasmic domain. When these residues are phosphorylated, they form binding site nuclei cores for adaptor proteins, such as, Src, Shc and growth factor receptor-bound protein *2* (Grb2) – leading to the activation of signal transduction pathways that culminate in cell survival/differentiation effects [194].

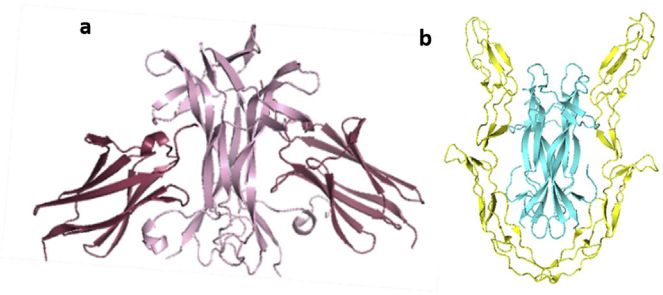

Fig. 9. Neurotrophic factor related receptors. a) Image of 1HCF [195], obtained by Pymol. Structure of TrkB-d5 bound to neurotrophin-4/5, from *Homo sapiens*, expressed in *Escherichia coli* BL21. The purple chains represent the neurotrophic receptor TrkB, which is complexed with its ligand, NT4. b) Image of 3BUK [196] obtained by Pymol. Structure of the Neurotrophin-3 and $p75^{NTR}$ symmetrical Complex, from *Rattus norvegicus* and *Homo sapiens*, expressed in *Spodoptera frugiperda* and *Escherichia coli*. The yellow chains represent the neurotrophic receptor $p75^{NTR}$ and the blue chains show the neurotrohic protein NT3. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The $p75^{NTR}$ (Fig. 9b) [196] is a transmembrane glycoprotein and a member of the superfamily of tumour necrosis factor-α (TNF-α) receptors, having an extracellular domain with four cysteine-rich domains (CRD), two of which bind to NTF, and a cell death domain in the intracellular region [196]. The mature pro-NTF and NTF ligands form homodimers that bind to the $p75^{NTR}$ dimeric receptor – which regulates multifunctional cellular processes by modulating Trk signalling and recruitment of adaptor molecules, *viz.*: receptor-associated necrosis factor 1–6 (TRAF 1–6); neurotrophin (NT) receptor interacting MAGE homolog (NRAGE); neurotrophin (NT) receptor interacting factor (NRIF); and receptor interacting protein 2 (RIP2). These adaptor molecules are dependent on the ligand and, according to the existing co-receptor, determine which signalling pathways will be activated. It should also be noted that elevated levels of NTF and/or low levels of Trk promote interactions between $p75^{NTR}$ and TRAF 1–6, NRAGE and NRIF – leading to the activation of the *c*-Jun NH_2-terminal kinases (JNK) pathway and cell death [194].

In AD, an increase in $p75^{NTR}$ expression in neurons from the CA1 and CA2 areas of the human brain hippocampus and in rat models

Table 7
Natural products acting on receptors for advanced glycation end-product receptors (RAGE). Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
(+)-Catechin (**114**), (−)-Epicatechin (**115**) and Proanthocyanidin B2 (**116**) (*Cinnamomum zeylanicum* Blume)	Flavonoids	Inhibitory effects on AGEs formation, due to their antioxidant properties and ability to capture reactive carbonyl species intermediates of AGE	[189]
trans-Resveratrol (**58**) (grapes, peanuts, blueberries and dark chocolate)	Stilbene	Reduction of RAGE expression in the hippocampus, decreasing Aβ accumulation	[190]
Chrysin (**117**) (*Passiflora caerulea* L.)	Flavonoid	Inhibition of AGE/RAGE signalling and consequent oxidative stress, attenuating apoptosis of cells	[191]
Ginsenosides Rg1 (**118**), Rb1 (**119**), Rh1 (**120**), Rb2 (**121**), and Rc (**122**) (*Panax ginseng* C.A. Mey.)	Triterpene saponins	Decreases regulation of the RAGE signalling pathway	[192]
Glycyrrhizic acid (**123**) (*Glycyrrhiza glabra* L.)	Triterpene glycoside	Downregulation of RAGE expression, decreasing of circulating AGE by upregulation of soluble RAGE which enhance the scavenging and clearance of AGEs.	[193]

was observed. In addition, the aggregates of Aβ peptides were found to bind to the $p75^{NTR}$ receptor and to form immunoprecipitates – which could be directly responsible for the activation of $p75^{NTR}$-mediated cell death. The $p75^{NTR}$ binds to mature NTF and pro-NTF ligands, with similar affinity but different kinetics, and all these substrates have a variety of biological effects. In particular, the biological functions of these $p75^{NTR}$ may be related to the fact that they act as co-receptors of TrkA and mediate several neurobiological functions, such as cell survival/death. Therefore, they appear to be very important in diseases, being highly over-regulated in neurodegenerative pathologies. In fact, as the disease progresses with age, a greater expression of $p75^{NTR}$ and a lower expression of Trk are observed. Activation of $p75^{NTR}$ signalling pathways increases β-secretase expression and accelerates the production of Aβ peptide aggregates, although their aggregation is inhibited through the extracellular domain [15,24,197].

In HD, changes in the production of BDNF are observed owing to the mutant huntingtin protein, and since the binding of BDNF to TrkB is required for the survival of neurons, this leads to brain striatum degeneration. Moreover, there is a decrease in mRNA encoding TrkB and an increase in $p75^{NTR}$ mRNA. With respect to PD, a direct correlation is found between the decrease of BDNF and NGF, the neurodegeneration of dopaminergic neurons, and the expression of TrkB and $p75^{NTR}$ [24,194].

As shown in Table 8 one may find naturally occurring compounds exerting their biological effects on these Trk, either by direct agonism of TrkB receptors (as in the case of 7,8-dihydroxyflavone (**124**, Fig. S1) or deoxygedunin (**125**, Fig. S1)) or by stimulating the expression of TrkB (promoted by hyperforin (**126**, Fig. S1)) [24,53,198–200]. Such bioactivity has been evaluated through *in vitro* and *in vivo* (rats) models – and emphasizes the importance to undertake further studies to discover new agonists of TrK receptors and $p75^{NTR}$ antagonists. Particularly, molecular docking studies performed with 7,8-dihydroxyflavone (**124**, Fig. S1) and TrkB receptors revealed the presence of 3 H-bonds at the Ig2 domain of extracellular regions, in addition to interactions of **124** with the cysteine cluster 2 region of TrkB, like BDNF-TrkB interaction, thus contributing to the receptor dimerization, enhanced TrkB phosphorylation and promotion of downstream cellular signalling. Molecular analysis showed that 7,8-dihydroxyflavone is involved in hydrogen bonding with Leu315, Lys312 as well as Pro313; and a π-σ interaction occurs between B ring of the compound and C265 of Leu315 [201].

5. Immune system related receptors

Although the inflammatory response is not typically a factor in the initiation of neurodegenerative diseases, there are evidences (in animal models) that the inflammatory responses involving microglia, resident macrophages in the brain and spinal cord – which are the first line of defence of the innate immune system – contribute for disease progression. Microglia cells control the cellular environment and produce factors that influence neighbour astrocytes and neurons, such as NTFs and anti-inflammatory factors [23,202,203].

For an effective immune response, the initial detection of the pathogen should be amplified from the recruitment of other cells to the site of infection, which induce antimicrobial activities and initiate the development of adaptive immunity. To that purpose, several genes are activated, such as those encoding cytokine amplifying molecules (*e.g.* TNF-α, and the Interleukin-1 β (IL-1β)] and chemokines that act as a concentration gradient in order to recruit other cells. In addition, genes encoding proteins with antimicrobial activity – such as iNOS – and enzymes that generate ROS – such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase – are activated. The latter is an example of a system that results in side effects in cells of the brain parenchyma [23]. In turn, elevated •NO levels induce neurotoxic effects due to peroxynitrite ($ONOO^-$) formation [204].

In AD, Aβ peptide aggregates are detected by microglia cells and astrocytes through various sensors, such as toll-like receptors (TLRs), inducing the production of ROS, •NO, TNF-α, IL-1β, among other factors that promote neuronal death [23]. In PD, the aggregation of α-synuclein fibrillary proteins activates microglia cells, enhancing the neurotoxicity of dopamine [205].

Inflammatory responses are usually initiated by pattern recognition receptors (PRRs) that bind to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which consist in strange signs to the cell [23,206]. One known class of PRRs is the TLR, which is present in microglia and bind to pathogenic molecules not found in the host. There are 10 TLRs in humans. TLR1, TLR2, TLR4-TLR6, and TLR10 are located on the plasma membrane and primarily recognize microbial membrane components. TLR3, TLR7-TLR9 are found in the lumen of endocytic compartments, the location where uptaken microbial components are directed, and where TLRs recognize aberrant (microbial or autoimmune) nucleic acids [207]. Particularly, the TLR4 binds to lipopolysaccharides (LPS) of Gram-negative bacteria, and evidences in transgenic mouse models showed that TLR4 polymorphisms are also found on the basis of neurodegenerative diseases – such as AD – through binding to the Aβ peptide aggregates [23,206]. There is evidence that TLR4 alone is not enough to recognize LPS, requiring the co-receptor myeloid differentiation protein 2 (MD-2) to sense the lipid A domain of LPS. MD-2 is a small protein containing 143 amino acid residues that adopt a β cup fold with two antiparallel β sheets and constructs a hydrophobic pocket. The engagement of LPS with TLR4–MD-2 complexes leads to the dimerization of two TLR4–MD-2 complexes and the activated receptor multimer recruits two major adaptor molecules, myeloid differentiation factor (MyD88) and TIR domain containing adaptor-

Table 8
Natural products interacting with receptors associated with neurotrophic factors (NTF). Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
7,8-Dihydroxyflavone (**124**) (Present in several plants such as *Tridax procumbens* L., *Godmania aesculifolia* (Kunth) Standl. and *Primula* sp.)	Flavonoid	Direct receptor agonist of TrK, mimicking neurotrophin binding; Induces the dimerization as well as phosphorylation of the TrkB and consequent Akt and ErK1/2 signalling pathways	[24,198]
Huperzine *A* (**42**) (*Huperzia serrata* (Thunb.) Trevis.)	Alkaloid	Increases BDNF/TrkB signalling, dependent of PI3/protein kinase *B* (AkT)/ mammalian target of Rapamycin (mTOR) pathways; Increase of the production of NGF, BDNF and phosphorylated MAPK.	[53,198]
Deoxygedunin (**125**) (*Azadirachta indica* A. Juss)	Terpenoid	Agonist of TrkB, through the mimesis of BDNF's biological activities. Protection of the neurons from the apoptosis in a TrkB dependent manner.	[198,199]
Hyperforin (**126**) (*Hypericum perforatum* L.)	Phloroglucinol derivative	Stimulation of expression of TrkB	[198,200]

inducing interferon-β (IFN-β) (TRIF) [208].

Regarding the structure of TLR4s (Fig. 10) [209] they consist of type *1* transmembrane proteins with an extracellular domain composed of leucine-rich repeats (typically 19–25) that mediate ligand recognition and the receptor dimerization, whose domains sandwiching the ligands and cause the closing of extracellular and intracellular domains. Besides that, they contain a transmembrane domain and a toll/interleukin-11 receptor (TIR/IL-11) domain – essential for the signal transduction mechanism through homotypic interaction of the ligands [207,210].

The binding to PRR leads to the activation of signal transduction mechanisms that result in the activation of transcription factors – such as NF-κB – and kinases – such as MAPK. To that purpose, the TLR associate to adaptor proteins referred above, such as MyD88 and TRIF [23].

Another class of PRR, which is also involved in sensitivity to Aβ peptide aggregates is NOD-like receptors (NLRs). While TLRs are transmembrane, NLRs consist of soluble cytoplasmic receptors that act as cell damage sensors and their structure reveal a common domain organization with a central NOD, a N-terminal effector domain, and C-terminal leucine-rich repeats (LRRs) [211]. In AD, Aβ oligomers and fibrils induce lysosomal degradation and the release of NACHT, LRR and PYD domains-containing protein 3 (NALP3), also known as cryopyrin, expressed in microglia, that activates signal mechanisms, such as the activation of caspases that culminate in apoptosis and maturation of pro-inflammatory mediators, such as IL-1β [23,212].

With respect to the natural products that act on the immune system receptors (Table 9) [16,36,37,57,213–218] studies have shown that phenolic compounds, such as *trans*-resveratrol (**58**, Fig. S1), curcumin (**50**, Fig. S1), chlorogenic acid (**127**, Fig. S1), baicalin (**128**, Fig. S1), naringenin (**129**, Fig. S1), (−)-epigallocatechin-3-gallate (**74**, Fig. S1), magnolol (**69**, Fig. S1) and honokiol (**70**, Fig. S1) can be used for the treatment of neuro-inflammation, for example through the regulation of TLR2 and TLR4 [213]. They also act against oxidative stress – through direct action against free radicals, or by activation of regulatory pathways – through modulation of signal cascades or overexpression of genes [204]. Other compounds with great importance are TLR4 antagonists, which includes lipopolysaccharides (**130**–**132**, Fig. S1), berberine (**136**, Fig. S1), atractylenolide I (**137**, Fig. S1) and zhankuic acid A (**138**, Fig. S1). On the other hand, morphine (**142**, Fig. S1) act as TLR4 receptor agonist.

Wang et al. [208] explored the binding mechanism of curcumin (**50**, Fig. S1) to MD-2 by molecular docking and molecular dynamic simulations. Curcumin occupies a large part of the LPS binding site at the large hydrophobic binding pocket of MD-2. This natural compound can establish multiple H-bonds with the amino acids Arg90, Glu92 and Tyr102 of MD-2, mainly through oxygen atoms in hydroxyl and methoxy groups (O3 and O5). Moreover, Peluso et al. [219] also reported that xanthohumol (**135**, Fig. S1) have the same interaction with Tyr102, highlighting that this amino acid is crucial for MD2-ligand binding.

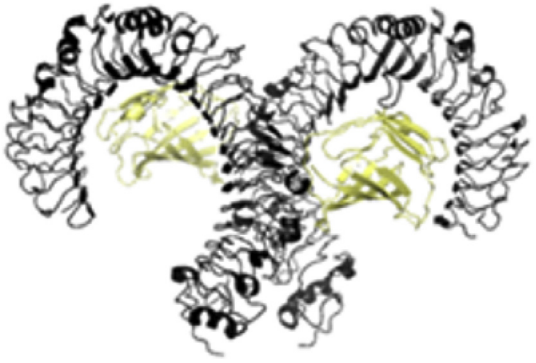

Fig. 10. Image of 3FXI [209] obtained by Pymol. Structure of the human TLR4. The yellow chains represent the ligands. In this case, shows the lymphocyte antigen 96. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

6. Oxidative stress related receptors

Scavenger receptors (SCARs) are a diverse family of pattern recognition receptors (PRRs) that are expressed primarily in astrocytes and microglia and are involved in the uptake of several substrates, namely oxidized proteins, lipids and apoptotic cells [16]. The receptor-ligand interaction triggers endocytosis, phagocytosis, adhesion and signalling processes, often depending on the collaboration of non-scavenger receptors such as TLRs [182,220].

These receptors have been classified into six classes, although there are some unclassified members remaining. They are all defined by high affinity and specificity for polyanionic ligands [182]. Class *A* scavenger receptors (SCARA) comprises the receptors that are involved in the defence against bacteria l and viral pathogens. Particularly, there are high levels of SCARA member *1* (SCARA-1) in the microglial cells around the Aβ plates. Another member is the macrophage receptor with collagenous structure (MARCO) that forms complexes with *N*-formyl peptide receptor *2* (FPRL2) by encountering Aβ peptides, then occurring intracellular signalling through ErK 1/2 and subsequent inhibition of cAMP [182,221]. The SCARA-1 structure consists of an arrangement of three coiled extracellular regions with cysteine-rich domains connected to the plasma membrane through a long fibrous “stem” composed of an α-helix coil and a triple collagen helix, which is likely to be involved in the binding to substrates through the collagen-like domain [182].

The class *B* scavenger receptors (SCARB) provide a response against bacteria and fungi and, in AD, a high level of SCARB-1 expression is associated with increased Aβ peptide deposition. In addition, cluster of differentiation *36* (CD36)/SCARB member *2* (SCARB-2) is also expressed in microglia and consists of a receptor that is activated by Aβ peptide binding, activating the cells to produce cytokines and chemokines that induce the migration of other cells. It is also worth noting that CD36 can also form heterodimeric complexes with TLR-4 and TLR-6, resulting in the production of ROS and in an increase of mRNA of IL-1β, indicative of the activation of inflammasomes. The SCARB structure (Fig. 11) [222] is characterized by the presence of the membrane-bound nitrogen (*N*) and carbon (*C*) terminals and an extracellular wide loop [182,223]. The class *C* scavenger receptors (SCARC) are involved in the phagocytosis of Gram-negative and Gram-positive bacteria, whereas SCARE contain lectin domains. The relation between SCARC and neurodegenerative diseases is unknown [182]. Class *D* scavenger receptors (SCARD) are characterized by the presence of an extracellular mucin domain. In AD, there is over-regulation of CD68/SCARD1 in microglial cells [182,224]. Finally, class *F* scavenger receptors (SCARF) are distinguished by multiple extracellular replicates and class *F* scavenger receptor member 1 (SCARF-1) is also involved in the pathogenesis of AD [181,224]. As summarized in Table 10 there are natural compounds which act essentially by decreasing the regulation of the scavenger receptors, such as (−)-epigallocatechin-3-gallate (**74**, Fig. S1), secoiridoids, vitamin E (**109**, Fig. S1), curcumin (**50**, Figs. S1), 3,5,6,7,8,3′,4′-heptamethoxyflavone (**145**, Fig. S1) and 3,6,7,8,3′,4′-hexamethoxyflavone (**146**, Fig. S1) [225–233]. Tannic acid (**147**, Fig. S1) and sennoside B (**148**, Fig. S1) are able to reduce SRA mediated antigen transfer, while

Table 9
Natural products that interact with immune system receptors. Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
trans-Resveratrol (**58**) (grapes, peanuts, blueberries and dark chocolate)	Stilbene	Downregulation of important enzymes and cytokines in inflammatory signalling pathways; Acts in upstream in the activation of the cascade by interfering in the oligomerization of TLR4 after binding to the receptors	[16,213,214]
Curcumin (**50**) (*Curcuma longa* L.)	Curcuminoid (diarylheptanoid)	Attenuates the homodimerization of TLR4, necessary for triggering the signalling cascade pathways; Overexpression of inflammatory mediators that inhibit the TLR4- MAPK/NF-κB pathway; Blocks the intracellular production of ROS linked to NADPH oxidase	[36,37,213]
Chlorogenic acid (**127**) (Compound present in coffee, tea, and in the leaves and fruits of several plants, such as apples, pears, carrots, tomatoes, and sweet potatoes)	Hydroxycinnamic acid	Attenuates mRNA levels and protein expression levels of pro-inflammatory mediators; suppresses of TLR4-mediated NF-κB signalling pathway; reduces the levels of pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1β	[213,217]
Baicalin (**128**) (*Scutellaria baicalensis* Georgi)	Flavonoid	Inhibits the TLR2/4 signalling pathway, reducing the expression of NF-κB, inducible NOS (iNOS) and COX-2	[16,163]
Naringenin (**129**) (Citrus fruits, such as *Citrus sinensis* (L.) Osbeck)	Flavonoid	Downregulation of TLR2 and TLR4 protein expression and TLR2 mRNA levels	[215]
(−)-Epigallocatechin-3-gallate (EGCG) (**74**) (*Camellia sinensis* L.)	Flavonoid	Decreases regulation of the inflammatory response of macrophages; Inhibits the production of TNF-α, IL-1β, IL-6 induced by LPS; Stimulates the activation of Nrf2, eliminating or inactivating ROS; Inhibition of TLR4 signal downstream	[16,37,213]
Magnolol (**69**) and honokiol (**70**) (*Magnolia* spp.)	Lignans	Inhibition of TLR4 expression up-regulated by LPS, supressing NF-κB activation and proinflammatory cytokine expression	[57,218]
Lipopolysaccharides and lipid A (**130**) (*Rhodobacter sphaeroides*)	Lipopolysaccharide	Antagonists of TLR4, blocking the formation of the TLR4/ myeloid differentiation factor 2 (MD-2) complex	[36]
Lipooligossaccharide (**131**) from *Bartonella quintana*	Lipopolysaccharide	Antagonists of TLR4, blocking the formation of the TLR4/ MD-2 complex	[36]
Lipopolysaccharide (lipid A displayed in structure **132**) (*Oscillatoria planktothrix FP1)*	Lipopolysaccharide	Antagonists of TLR4, blocking the formation of the TLR4/ MD-2 complex	[36]
Sulforaphane (**133**) and iberin (**134**) (*Brassica* spp.)	Isothiocyanates	Antagonists of TLR4, blocking the formation of the TLR4/ MD-2 complex; Sulforaphane also suppress the LPS-induced expression of inflammatory genes	[36,37]
Xanthohumol (**135**) (hops and beer)	Prenylated chalcone	Antagonists of TLR4, blocking the formation of the TLR4/ MD-2 complex	[36]
Celastrol (**93**) (*Tripterygium wilfordii* Hook.f. and *Celastrus scandens* Lime)	Triterpenoid	Antagonists of TLR4, blocking the formation of the TLR4/ MD-2 complex	[36]
Berberine (**136**) (*Berberis* spp.)	Alkaloid	Antagonists of TLR4	[36]
Atractylenolide I (**137**) (*Atractylodes lancea* (Thunb.) DC)	Sesquiterpene	Antagonists of TLR4	[36]
Zhankuic acid A (**138**) (*Taiwan fungus camphoratus)*	Sterols	Antagonists of TLR4	[36]
Cinnamaldehyde (**139**) (*Cinnamomum* spp.)	Aldehyde	Inhibition of the activation of NF-κB and IRF3 induced by LPS; Inhibition of TLR4 oligomerization by LPS	[37]
1-Dehydro-10-gingerdione (**140**) (*Zingiber officinale* Rosc.)	Phenolic compound	Potent inhibitor of LPS-MD2 interaction; Supresses MyD88 dependent NF-κB and Ap1 activation and TRIF-dependent pathway.	[37]
Glycyrrhizic acid (**123**) and isoliquiritigenin (**40**) (*Glycyrrhiza* plants, such as as *G.uralensis* Fisch. ex DC.)	Triterpenic saponin (Glycyrrhizic acid), flavonoid (isoliquiritigenin)	Inhibition of NF-κB and MAPK activation, mediated by the oligomerization of TLR4/MD2, resulting in a decreasing of production of proinflammatory cytokines	[37]
Paclitaxel (**141**) (*Taxus brevifolia* Nutt.)	Diterpene alkaloid	Blocking of NF-κB activation and cytokines expression by binding MD2 antagonist, ameliorating TLR4 dependent pathologies	[37]
Morphine (**142**) (*Papaver somniferum* L.)	Alkaloid	Agonist action on TLR4 receptors	[37]
Chitohexose (**143**) (helminths surface glycans)	Sugar	Actuation on TLR4 signalling, by competition with LPS as an antagonist	[37]
Oxyresveratrol (**144**) (*Morus alba* L.)	Stilbene	Inhibits the activation of NALP3	[216]

rhein (**149**, Fig. S1) can partially dissociate or antagonize SCARA oligomerization. Docking and molecular dynamic simulations of the binding of tannic acid (**147**, Fig. S1), sennoside B (**148**, Fig. S1) and rhein (**149**, Fig. S1) to SCARA showed that Arg351, Ile365, Leu366, Ser390 and Ser425 are critical residues for binding of these ligands to SCARA. Mostly, Ile365, Ile426 and Ile 431 of one subunit form a hydrophobic cavity that interact with rhein backbone together with the Arg351 residue from the other subunit. Moreover, the side chains of Ser390 and Ser425 act as H-bond donors and Leu366 backbone carbonyl and Glu427 side chain serve as H-bond acceptors. These are common features for all these three ligands. Besides these features, for sennoside B, His367 and Trp434 seems to be involved in aromatic stacking interaction with the backbone of the molecule, whereas Val350, Ile365 and Ile426 reinforce the hydrophobic interaction with sennoside B. Sennoside B also establishes water mediated interactions with Arg351. In the case of rhein, similar interactions involve Arg389 and the hydroxyl group of the ligand [231,232].

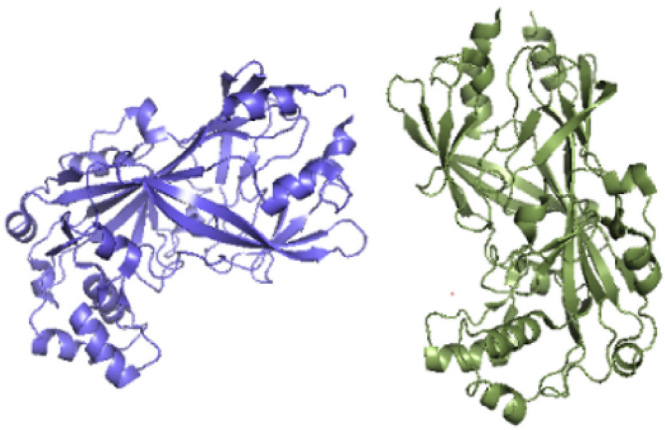

Fig. 11. Structure of scavenger receptors. Image of 4TVZ [222] obtained by Pymol. Structure of human SCARB2 in Neural Condition (pH 7.5).

7. Transcription factors regulating gene expression related receptors

Peroxisome proliferator-activated receptors (PPARs) belong to the superfamily of steroid hormone receptors. They are a group of nuclear receptor proteins that function as transcription factors regulating gene expression. They play an important role in cell differentiation, cell development, and metabolism (lipid peroxidation) and are activated by gene expression regulatory ligands [4,5]. There are three classes of PPARs that are expressed in the brain – *viz*. PPAR-α, PPAR-β/δ and PPAR-γ – the latter two being the most abundant [5]. Similar to the other nuclear receptors, the three subtypes have in common N-terminal transactivation domains, central highly conserved deoxyribonucleic acid (DNA)-binding domains, and C-terminal ligand-binding domains (LBDs) (Fig. 12) [234,235].

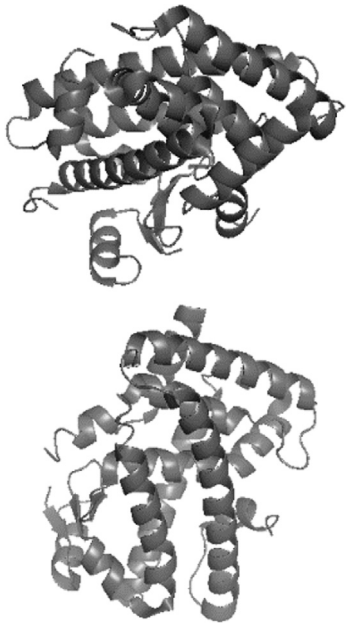

Fig. 12. Image of 3D5F [234] obtained by Pymol. Structure of the human PPAR-δ complex.

Metabolic pathways are regulated at different levels in response to environmental or hormonal factors. Thus, PPAR-α promotes the metabolism and catabolism of fatty acids by overregulating the genes involved in the transport of fatty acids and their oxidation. In turn, PPAR-β/δ is responsible for the regulation of lipid and glucose metabolism. Finally, PPAR-γ is related to glucose metabolism and regulation of fatty acid storage, insulin sensitivity and cell growth [236,237].

Table 10
Natural products that interact with the scavenger receptors associated with oxidative stress. Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
(−)-Epigallocatechin-3-gallate (EGCG) (**74**) (*Camellia sinensis* L.)	Flavonoid	Stimulation of nuclear factor κB (NF-κB) subunit translocation, leading to decreasing of scavenger receptor *A* (SCAR-A) expression, by suppressing the activity of its promoter zone	[225]
Secoiridoids and their glycosides *(Gentiana scabra* Bunge)	Secoiridoids	Decreases SCAR-A regulation by significantly reducing extracellular signal-regulated kinase (ErK) activity in macrophages	[226]
Vitamin *E* (or α-tocopherol) (**109**) (Compound present in vegetable oils, nuts, whole grains and green leafy vegetables)	Tocopherol	Decreases SCAR-A expression in macrophages; Decreases mRNA expression and protein expression of cluster of differentiation *36* (CD36) (a type SR-B)	[227]
Curcumin (**50**) (*Curcuma longa* L.)	Diarilheptanoid (Curcuminoid)	Decreases SCAR-A protein expression; No effect on CD36 protein expression	[228]
Nobiletin (**43**) (*Citrus aurantium* L.)	Flavonoid	Specific SCAR-A inhibition, without affecting protein levels or expression of plasma membrane receptors	[229]
3,5,6,7,8,3′,4′-Heptamethoxyflavone (**145**) and 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone (**146**) (Citrus fruits, such as *Citrus sinensis* L.)	Flavonoids	Inhibitory effect of 3,5,6,7,8,3′,4′-heptamethoxyflavone in oxLDL-mediated scavenger receptor expression, by decreasing of CD36 mRNA expression. 5-Hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone reduces the oxLDL uptake but have no effect in downregulation of CD36 mRNA or proteic expression, instead have effect in downregulation of SCAR-A.	[230]
Tannic acid (**147**) (bark of hemlock, chestnut, mangrove, and oak trees)	Tannin	Reduction of antigen transfer by SCARA receptor	[231]
Sennoside B (**148**) (*Cassia senna* L.)	Anthranoid	Reduction of antigen transfer by SCARA receptor	[231,232]
Rhein (cassic acid) (**149**) (*Cassia senna* L.)	Anthraquinone	Partial dissociation or antagonism of SCARA oligomerization	[231,232]
Fucoidan (**150**) (brown seaweeds as *Fucus vesiculosus* L.)	Sulfated polysaccharide	Antagonist of SCAR-A	[233]
Ginsenoside Rg3 (**151**) (*Panax ginseng* C.A. Mey)	Triterpene saponin	Increase the expression of macrophage SCAR-A	[273]

In relation to inflammatory processes, PPARs are also able to regulate the activation of transcription factors – such as NF-κB – and oxidative pathways. Activation of PPAR-α prevents the synthesis and release of cytokines or the induction of inflammatory mediators such as COX-2 or adhesion proteins. In turn, the activation of PPAR-γ also reduces NOS and COX-2 expression and pro-inflammatory cytokines. Besides, PPAR-α and PPAR-γ can inhibit the activation of macrophages and glia cells that contribute to inflammatory processes and consequently to neuronal death [237,238].

In AD, the development of PPAR-α agonists is associated with a slower cognitive decline, whereas PPAR-γ agonists are involved in the inhibition of Aβ-induced inflammation as well as in the release of Aβ peptide [237,238]. In PD, PPAR-γ agonists attenuate the activation of glia cells and prevent the loss of dopaminergic cells in substance nigra, by induction of intracellular nuclear transcription factor κBα (IκBα), blockade of NF-κB activation and •NO production. Table 11 enumerates natural compounds that activate or increase the expression of PPAR- γ or PPAR-α. It is worth to mention the class of flavonoids, which includes icariin (**159**, Fig. S1), luteolin (**25**, Fig. S1), quercetin (**160**, Fig. S1), kaempferol (**161**, Fig. S1), (−)-catechin (**162**, Fig. S1), 2′-hydroxychalcone (**163**, Fig. S1), biochanin A (**164**, Fig. S1), genistein (**165**, Fig. S1), 6-hydroxydaidzein (**166**, Fig. S1), among others, as well as the stilbenes *trans*-resveratrol (**58**, Fig. S1) and amorphastilbol (**168**, Fig. S1), the monoterpene (±)-linalool (**152**, Fig. S1), the carotenoids sargaquinoic acid (**153**, Fig. S1) and sargahydroquinoic acid (**154**, Fig. S1), the coumarin osthol (**155**, Fig. S1) and the alkaloid chelerythrine (**94**, Fig. S1) [16,235,239–253]. Concerning the interaction of PPAR-γ to the ligands, it is important to underline the fact that LBD of the receptor is a large Y-shaped cavity composed by an entrance domain, constituted by amino acids as Ala292, Met329, Leu330 and Leu333; and two pockets, arm I, substantially polar (presence of amino acids as Cys285, Ser289, His323, His449 and Tyr473) and arm II, mainly hydrophobic, thus allowing flexibility for the ligand binding [244,247]. Also, the LBD is constituted by 13 α-helices and a small four-stranded β-sheet, emphasising that H12 belongs to the ligand-dependent activation domain (activation function-2, AF-2) which is essential for ligand binding and PPAR function. H12 and the loop between H2′ and H3 are the most mobile parts of LBD [247]. According to the literature, PPAR-γ partial agonists bind only to β sub-pocket, while full agonists always occupy both AF-2 and β-

Table 11
Natural products that interact with peroxisome proliferator-activated receptors (PPAR). Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
trans-Resveratrol (**58**) (grapes, peanuts, blueberries and dark chocolate)	Stilbene	Increases levels of PPAR-γ; Direct activation of PPAR-α through the 4′–OH group of the compound	[16,235]
(±)-Linalool (**152**) (Found in essential oils of over 200 species belonging to Lamiaceae, Lauraceae family, and Rutaceae families)	Terpene	Direct ligand of PPAR-α, reducing cellular lipid accumulation, inducing oxidation of fatty acids and significantly reducing the concentrations of saturated fatty acids	[235]
Sargaquinoic acid (**153**) and sargahydroquinoic acid (**154**) (Seaweed *Sargassum yezoense* (Yamada) Yoshida & T.Konno)	Carotenoids	Dual agonists of PPAR-α and PPAR-γ with a slight effect on PPAR-δ	[235]
Osthol (**155**) (*Cnidium monnieri* (L.) Cusson ex Juss., and *Angelica pubescens* Maxim.)	Coumarin	Activation of PPAR-α through an AMPK-dependent pathway that induces receptor phosphorylation	[235]
Hesperetin (**156**), naringenin (**129**) and its glycosides (**157**, **158**) (Compounds of *Citrus* species, such as *C. sinensis* (L.) Osbeck.)	Flavonoids	All compounds induce the expression of PPAR-γ in a dose-dependent manner; Naringenin activates the PPAR-α	[235]
Icariin (**159**) (*Epimedium brevicornum* Maxim.)	Flavonoid	Over-regulation of PPAR-α and PPAR-γ; Inhibition of NF-κB expression	[235]
Chelerythrine (**94**) (*Chelidonium majus*,L.)	Alkaloid	Potent binding to PPAR-α, by blocking the CDK-5-mediated phosphorylation of the receptor.	[246]
Luteolin (**25**) (Compound present in various types of plants, as fruits, vegetables and medicinal herbs)	Flavonoid	Weak partial agonist/antagonist of PPAR-γ; activates PPARγ-dependent reporter gene expression as partial agonist;	[247,248]
Quercetin (**160**) (Compound of fruits and vegetables)	Flavonoid	Binds to PPAR-γ; activates PPARγ-dependent reporter gene expression as partial agonist	[247,249]
Kaempferol (**161**) (Compound found in fruits and vegetables)	Flavonoid	Binds to PPAR-γ; activates PPARγ-dependent reporter gene expression as partial agonist	[247,250]
(−)-Catechin (**162**) (*Camellia sinensis* (L.) Kuntze)	Flavonoid	Binds to purified PPAR-γ; activates PPARγ-dependent reporter gene expression as full agonist	[247,251]
2′-Hydroxychalcone (**163**) (*Cinnamomum* spp.)	Flavonoid	Binds to PPAR-γ; activates PPARγ-dependent reporter gene expression as partial agonist	[247,252,253]
Biochanin A (**164**) (*Trifolium pratense* L.)	Flavonoid	Binds to PPAR-γ; activates PPARγ-dependent reporter gene expression as partial agonist	[239,247]
Genistein (**165**) (*Glycine max* (L.) Merr.)	Flavonoid	Binds to PPAR-γ; activates PPARγ-dependent reporter gene expression as partial agonist; Activation of PPAR-α	[240,247]
6-Hydroxydaidzein (**166**) (*Glycine max* (L.) Merr.)	Flavonoid	Binds to purified PPAR-γ; activates PPARγ-dependent reporter gene expression as full agonist	[241,247]
6′-Hydroxy-O-desmethylangolensin (**167**) (*Trifolium pratense* L.)	Flavonoid	Binds to PPAR-γ; activates PPARγ-dependent reporter gene expression as partial agonist	[242,247]
Magnolol (69) and honokiol (**70**) (*Magnolia officinalis* Rehder & Wilson)	Neolignan	Binds to PPAR-γ; activates PPARγ-dependent reporter gene expression as agonist	[243,244,247]
Amorphastilbol (**168**) (*Robinia pseudoacacia* var. *umbraculifera*)	Stilbene	Dual agonist of PPAR-α and PPAR-γ	[245,247]
Amorfrutins 1, 2 and B (**169**,**170**,**171**) (*Amorpha fruticosa* L.)	Amorfrutins	Binds to PPAR-γ; activates PPARγ-dependent reporter gene expression as partial agonist	[247]
Falcarindiol (**172**) (*Notopterygium incisum* C.T.Ting ex H.T.Chan)	Polyacetylene	Binds to PPAR-γ; activates PPARγ-dependent reporter gene expression as partial agonist	[244,247]

sheet sub-pockets to activate PPAR-γ [243]. Therefore, compounds like amorfrutins 1, 2 and B (**169,170,171,** Fig. S1) which are partial agonists present high affinity due to the interaction of the carboxyl group to Ser342 of the β-sheet via hydrogen bonds, as well as binding to Arg288 of H3. Particularly, amorfrutin B (**171,** Fig. S1) shows significantly higher affinity due to its long geranyl side chain, which forms additional hydrophobic interactions to Arg288 of H3 [247]. Besides that, the compound luteolin (**25,** Fig. S1) interacts by two hydrogen bonds with Lys265 and His266 at the Ω loop that links H2′and H3 and makes hydrophobic contacts with various amino acids, as Phe264, Gly284, Phe287, Cys285, Arg288, Leu330, Ser342, Ile341, Met364, and Val339 [247,248]. Also, a water molecule seems to be involved on the binding of luteolin to the LBD [247]. In this case, luteolin (**25,** Fig. S1) occupies the region of PPAR-γ delimited by the H3 and the β-sheet, not contacting H12 [248]. Concerning magnolol (**69**, Fig. S1), two molecules of magnolol cooperatively occupy the PPAR-γ, since one molecule occupies AF2 through the hydroxyl group that makes a hydrogen bond with Ser289 in H3 and water-mediated bonds with Tyr473. The other molecule binds to the β-sheet, by a hydrogen bond between hydroxyl group of the magnolol and Ser342. Also, it exists a water-mediated hydrogen bond in the β-sheet to magnolol to further stabilize the ligand binding [243,247]. Additionally, the compound chelerythrine (**94**) establishes interactions with PPAR-γ mainly through a water molecule between the group methoxy of the compound and the carbonyl oxygen of the amide from Ile326. There is also a water-mediated bond within the nitrogen or carbonyl oxygen of an amide from Leu353, Phe360 and Met364 and the heterocyclic group of the chelerythrine [246].

8. Blood-brain barrier receptors

8.1. Apolipoprotein E (ApoE) or low-density lipoproteins (LDL)

One of the genetic variations of AD is related to an allelic variant of apolipoprotein *E* (ApoE, a 34 kDa protein) – which acts in part as a lipid transporter, existing three isoforms of ApoE, namely: ApoE2, ApoE3 and ApoE4 [23]. In brain, ApoE is mainly produced by microglia and astrocyte cells and plays important roles in binding to members of the low-density lipoprotein (LDL) receptor (LDLR) family – such as the classical LDLR and the pro-low-density lipoprotein receptor-related protein *1* (LRP1) – thereby making the chemical binding, the internalization and catabolism of lipoprotein neuronal development and for maintaining the plasticity and function of neurons [23,26].

At the cellular level, cholesterol secreted by glia cells through ApoE is incorporated into membrane compartments of neurons by endocytosis via LRP1. LRP1 is a 600 kDa multifunctional scavenger, transporter, signalling and endocytic receptor, highly expressed in brain – essentially in the cell bodies of neurons and dendritic cells, thus participating in cell signalling, as the activation of Ras/MAPK and AKT pathways [254]. LRP1 (Fig. 13) [255] consists of a non-covalent heterodimer composed by a heavy chain containing four putative binding domains as well as by a light chain containing a transmembrane domain and a cytoplasmic tail [26,256]. There are two forms of LRP1: one associated with the cell surface (LRP1) and another truncated soluble (sLRP1), normally found in plasma, resulting from the action of the enzyme β-secretase that cleaves the extracellular domain of LRP1 [25].

In the CNS, this type of receptor is correlated with neuronal stem cell proliferation and synaptic strength [254]. Besides that, LRP1 transports several ligands, such as Aβ peptides and ApoE-Aβ complexes, through the blood-brain barrier [25]. It is important to note that the expression of the latter is associated with high cholesterol levels and defects in Aβ release – leading to the accumulation of its

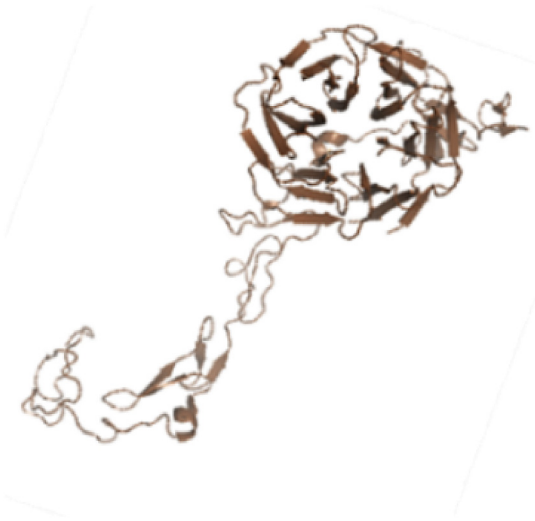

Fig. 13. Image of 3MOC [255] obtained by Pymol. Structure of human LDL receptor.

aggregates in brains of patients with AD [26]. In addition, lipoprotein receptors may contribute to AD through a decrease in LRP1 expression which, in turn, leads to changes in Aβ transport and, consequently, to the accumulation of such peptides in brain [25], as confirmed in AD mouse models subjected to LRP1 deletion, showing reduced plasma Aβ, elevated soluble brain Aβ, and deficits in spatial memory, thus emphasising the LRP1 function in systemic Aβ elimination [257]. On the other hand, the receptors may be related to the processing of APP [26]. Intensive research efforts are being conducted toward the development of novel therapies that act on LRP1, including the resource to natural products (Table 12) [230,258–264]. For instance, eicosapentaenoic acid (**173**, Fig. S1), docosahexaenoic acid (**102**, Fig. S1), 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone (**146**, Fig. S1) and curcumin (**50**, Fig. S1**)** affects LDLR expression and activity, particularly by activation of the receptors, thus increasing LDL levels and ApoE in brain, promoting the delivering of the cholesterol essential for the neuronal activity and decreasing the formation of amyloid protein levels in AD. However, several studies revealed that this beneficial effect was only observed in individuals who contains the ApoE4 allele [229,256,258,259,262,263].

9. Toxicity of natural compounds

It is worth underlining that there are natural compounds that also have toxic effects in humans and more studies are needed to establish the safe dose window. For example, despite the antioxidant effects of Δ9-THC (**76**, Fig. S1), it consists of a partial agonist of the CB1R and CB2R – which has damaging effects on memory – whose effect can be attenuated by another plant-based compound, the cannabidiol (**77**, Fig. S1). It has been demonstrated in animal studies that Δ9-THC induces dose-dependent toxicity and structural changes in brain regions rich in CB1Rs (hippocampus, amygdala, cerebellum, prefrontal cortex, and striatum). In humans, studies are not so consistent but changes in the hippocampus/parahippocampal complex and in the amygdala have often been reported [265]. Likewise, compounds such as epibatidine (**3**, Fig. S1), even being agonists of nAChR, are extremely toxic – thus, may only be at the base of the synthesis of analogues. Indeed, epibatidine causes hypertension, respiratory paralysis and seizures. Death occurs at doses not much higher than those required for antinociception [266].

Atropine (**22**, Fig. S1) and (−)-scopolamine (**23**, Fig. S1) act

Table 12
Natural products that interact with ApoE or LDL receptors. Structures of the compounds in Fig. S1.

Compound/Natural source	Compound class	Effect	Refs
Eicosapentaenoic acid (EPA) (**173**) and Docosahexaenoic acid (DHA) (**102**) (Active compounds of fish oil)	ω-3 fatty acids	LDLR downregulation. In individuals containing the ApoE4 allele, supplementation of elevated levels of DHA is associated with increased low-density lipoprotein (LDL) levels	[258,259]
Quercetin (**160**) (Compound present in several fruits and vegetables)	Flavonoid	Increase of ApoE levels and decrease amyloid-β (Aβ) protein levels	[260]
Vitamin *E* (α-tocopherol) **(109)** (Compound present in vegetable oils, nuts, whole grains and green leafy vegetables)	Tocopherol	Increases circulation of lipoprotein particles and LDL; Beneficial effects observed only in individuals not containing the ApoE4 allele	[261,262]
Curcumin (**50**) (*Curcuma longa* L.)	Curcuminoid	Increases LDLR mRNA expression resulting in an increase in plasma LDL-cholesterol uptake and consequently increases ApoE in brain	[263,264]
5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone (**146**) (citrus fruits, such as *Citrus sinensis* (L.) Osbeck)	Flavonoid	Upregulation of LDLR activity	[230]

pharmacologically via blocking mAChRs. The blockage of these receptors causes symptoms like tachycardia, dilated pupils, decreased gastrointestinal motility, dry hot skin and dry mouth due to a decreased sweat and saliva production. Apart from these peripheral effects, atropine also affects CNS and causes agitation, disorientation and hallucinations [267]. Cytisine (**2**, Fig. S1) binds with a high affinity to nAChRs. Like nicotine (**1**, Fig. S1), cytisine acts as a blocking agent on CNS via an over stimulation of these receptors. Thus, the symptoms of a poisoning are like a nicotine overdose, causing delirium and convulsions. Death can occur through a respiratory paralysis or failure of the circulatory system [267].

A large percentage of the users consume ibogaine (**11**, Fig. S1) for treatment of a substance-related disorder and, more than half, specifically for opioid withdrawal. The most prevalent side-effects of ibogaine are ataxia, tremors, muscle spasms, tonic–clonic seizures and severe nausea. A rise in blood pressure and a decline in pulse rate have been recorded 1–5 h after ibogaine administration. It was also reported one case in which permanent cognitive deficits and loss of vision remained for weeks after hospitalization. Death due to cardiotoxicity can occur [268].

Domoic acid (**63,** Fig. S1) is structurally similar to another known toxic, kainic acid, which activate iGluRs with the participation and co-activation of AMPARs (partial agonists)/KAs (agonists) and NDMARs receptor subtypes. In the brain, dendrites seem to be preferential early target sites for its excitotoxicity. The high concentration of iGluRs in the hippocampus and other brain regions provides targets for the selective cellular and structural excitotoxicity damage associated with domoic acid, leading to seizure and cognitive dysfunction. Also, it is observed an acute injury of astrocytes characterized by vacuolation and necrosis. Besides that, it was reported induction of the retinal injury caused by domoic acid, as well as spinal cord lesions characterized by focal hemorrhage, neuronal swelling and vacuolization in animals 1–2 h after domoic acid injection. Cardiovascular clinical manifestations were also observed due to the stimulation of NDMARs in the cardiomyocyte, leading to a Ca^{2+}, ROS and caspase-3 mediated pathway [269].

Another case is salvinorin A, which is a selective, high efficacy agonist at kappa-opioid receptors (KOPRs) [270]. For that reason, KOPR agonism in the temporal and parietal cortices could underlie the visual and auditory modifications (temporal cortex) and the altered experience of the body (parietal cortex), thus salvinorin A being a powerful hallucinogenic [270,271].

10. Conclusions

In recent years, several studies have demonstrated the importance of brain receptors in the mechanisms of neurodegenerative diseases. As illustrated in this revision manuscript, there is a huge variety of natural compounds that interact with brain receptors, exerting beneficial or toxic effects.

Flavonoids, such as epigalhocatechin-3-*O*-gallate, have a multiplicity of effects, namely: increasing $GABA_A$-mediated synaptic inhibition; mimicking the cellular effects of insulin; anti-inflammatory responses, such as the case of the inhibition of TNF-α and IL-1β production; MAPK and NF-κB inhibition; decreasing •NO production; and decreasing SCARA expression, among many other examples. It is important to underline that they may also exert effects at the level of DAR through increasing the levels of dopamine – as is an example the effect exerted by baicalein. Furthermore, the key role of resveratrol (stilbene) in numerous receptors such as RAGE, glutamate, insulin, IGFR and PPAR should also be highlighted.

On the other hand, terpenoids such as Δ9-tetrahydrocannabinol found in *Cannabis sativa* L. act as ROS scavengers or increase the activity of antioxidant enzymes. Regarding the alkaloids, this group includes compounds such as nicotine, anabaseine and muscarine that can act as agonists for nAChR and increase the beneficial properties resulting from their activation. Additionally, they may act by blocking excitotoxicity mediated by excessive activation of glutamate receptors, by activation of $GABA_A$Rs, by increased activation of dopamine receptors and by increase BDNF/TrkB signalling. With respect to tocopherols, such as vitamin E, they mediate processes such as increasing insulin signalling, decreasing oxidative stress, and decreasing regulation of SCARA as well as CD36 receptors. In addition, docosahexaenoic acid, an ω-3 fatty acid, reduces apoptosis of dopaminergic cells and leads to down-regulation of LRP1.

Nevertheless, it is worth underlining that there are natural compounds that also have toxic effects.

In short, the constant search for new natural compounds, their isolation, purification and characterization aim at attenuating symptoms associated with different neurodegenerative diseases. To that, comprehensive studies on brain receptors and associated biochemical mechanisms are required, so that their effects can be elucidated and novel applications can be unfolded.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2019.04.028.

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