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Review article

Natural terpenoids as a promising source for modulation of GABAergic system and treatment of neurological diseases

Azadeh Manayi [a], Seyed Mohammad Nabavi [b], Maria Daglia [c], Samineh Jafari [d,*]

[a] Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[b] Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[c] Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, University of Pavia, Pavia, Italy
[d] Department of Pharmacognosy, Faculty of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran

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ABSTRACT

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter reducing neural excitability in the mammalian central nervous system (CNS) with three subclasses of receptors. Several conventional drugs and compounds modulate the GABAergic system, demonstrating different pharmacological effects. In this review, interactions of natural terpenoids with the GABAergic system are highlighted with relation to disorders like anxiety, insomnia, convulsion, pain, and cognitive deficits. Terpenoids with various structures affect the function of the GABAergic system *via* dissimilar mechanisms. Most of the discussed compounds interact with GABA receptors, but especially with the $GABA_A$ subtype. This may be due to the fact that researchers tend to assess the interaction of compounds using $GABA_A$ receptors. However, bilobalide, a sesquiterpene, showed anticonvulsant properties through the activation of glutamic acid decarboxylase (GAD) enzyme, which is a key enzyme in biosynthesis of GABA. Therefore, further studies evaluating and comparing terpenoids of different classes and their interaction with the GABA system, along with their pharmacokinetic properties, could be worthwhile in future studies.

Contents

* Corresponding author.
E-mail address: jafari_s@zums.ac.ir (S. Jafari).

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Introduction

γ-Aminobutyric acid (GABA) is known to be a major inhibitory neurotransmitter in the central nervous system (CNS), mediating its function by interacting with three subclasses of receptors, $GABA_A$ and $GABA_C$ receptors that are ligand gated ion channels (ionotropic) and $GABA_B$ receptors that are a member of the superfamily of G protein-coupled receptors (metabotropic). Since $GABA_A$ receptors are the target of different therapeutics, they have attracted more notice. These receptors are composed of a chloride-gated channel formed by five protein subunits. The subunits can be selected from nineteen known families: α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, θ, π, and ρ_{1-3}. However, the prominent subunits in the $GABA_A$ heteropentameric structure are α_1, β_n, and γ_2. The less common subtypes possess δ, ε, or π subunits instead of the γ subunit or possess the θ subunit instead of the β subunit [1,2]. $2\alpha_1 2\beta_2\gamma_2$ is the most abundant subtype within the mammalian brain. Several positive and negative modulatory binding sites have been defined on it, therefore its recombinant forms are commonly used by researchers [3,4]. Different pharmacological compounds change the functions of a GABA receptor *via* binding to its modulatory sites. In other words, apart from the orthosteric site on a GABA receptor protein complex to which the primary ligand, GABA, binds, there are other allosteric binding sites for the modulators, such as benzodiazepines (BZD), barbiturates and so on. Other known targets for drugs modulating the GABA system are the enzymes involved in GABA synthesis and metabolism. For instance, a key enzyme in GABA biosynthesis from glutamic acid is glutamic acid decarboxylase (GAD). Another example is a key enzyme in GABA catabolism, GABA transaminase. Thus, agents such as pregabalin which enhances the activity of GAD and vigabatrin which inhibits GABA transaminase have been developed as antileptic therapeutics [5].

Some disorders such as anxiety, insomnia, pain and depression are often associated with low function of the GABAergic system. Thus, compounds which enhance GABA transmission, for example $GABA_A$ positive modulators, may have anxiolytic, sedative-hypnotic, analgesic and antidepressant properties. Enhancement of GABA inhibitory transmission also has a beneficial effect on epilepsy (a disorder which usually results from an imbalance between excitatory glutamatergic neurotransmission and inhibitory GABAergic transmission) [3,6]. Disturbances in the balance between GABA-mediated inhibition and glutamate-mediated excitation may also occur in disorders accompanied by cognitive deficits such as schizophrenia, Alzheimer's disease, and Down's syndrome [7,8]. GABA has two different effects on memory depending on its dose. In low doses this neurotransmitter inhibits memory, while in high doses it causes memory enhancement. This phenomenon may be attributed to differential activation of $GABA_A$ and $GABA_C$ receptors [9]. Negative modulation of $GABA_A$ receptors can improve memory and cognition and can be beneficial in schizophrenia, Alzheimer's disease, and Down's syndrome [8,10].

An increasing body of scientific literature indicates that many of the herbal medicines used for the treatment of CNS disorders contain compounds that affect the function of the GABAergic system [11]. Terpenoids are an important and structurally diverse group of natural compounds that are formed by the condensation of isoprene (5C) units. Based on the number of comprised isoprene units, terpenoids can be subdivided into different classes: monoterpenes (2 isoprene units), sesquiterpenes (3 isoprene units), diterpenes (4 isoprene units) and, triterpenes and steroids (6 isoprene units) [12,13]. This study aims to review the available evidence on the effects of natural terpenoids on the GABA system and their potential for treatment of CNS disorders.

Monoterpenes

Borneol

(+)- And (−)-borneol, bicyclic monoterpenes, are positive modulators of human recombinant $\alpha_1\beta_2\gamma_{2L}$ $GABA_A$ receptors at low concentrations of GABA. Different patterns of efficacy are demonstrated by the enantiomers, especially at low and high concentrations of GABA (1–100 μM). For instance, (+)-borneol at extremely high (100 μM) and low (1–4 μM) concentrations of GABA produces a greater enhancement in activity than (−)-borneol. At maximal GABA concentration (100 μM), inhibition occurs in response to (−)-borneol, indicating that the compound has a partial agonist activity, in the same manner as isoborneol. (+)-Borneol produces a statistically equivalent GABA response to the effects of pentobarbitone, propofol and etomidate at $\alpha_1\beta_2\gamma_{2L}$ receptors. The compound shows even greater effects than a neurosteroid, 5a-pregnan-3a-ol-20-one. The direct action of (+)-borneol is inhibited to some extent by bicuculline and picrotoxinin, $GABA_A$ receptor antagonists, suggesting that the compound may act at their respective binding sites among others. Since (+)-borneol is insensitive to flumazenil, a BZD antagonist, it is unlikely to bind to the high-affinity BZD site. The compound, however, may bind at the low-affinity BZD site [14]. Protective effects of (−)-borneol (50, 100, and 200 mg/kg, *ip*) in pentylenetetrazole (PTZ) and maximal electroshock (MES) tests were evaluated in mice. In the mammalian CNS, PTZ was found to antagonize GABA mediated postsynaptic inhibition and affect chloride permeability in the cellular membrane directly, inducing convulsion. Incidence of clonic PTZ convulsion is significantly reduced by pretreatment with (−)-borneol at all doses tested, and the latency of clonic convulsion is increased, antagonizing with flumazenil [15]. In contrast, the results of another study indicate that the compound possesses a positive modulation effect on the channel, unrelated to the $GABA_A$–BZD receptor [14]. Therefore, the results of previous studies on the binding of (−)-borneol to the $GABA_A$–BZD receptor are controversial. (−)-Borneol (100 and 200 mg/kg, *ip*) effectively prevents tonic convulsions induced by MES as well [15].