Therapeutic Potential of Myrtenal and Its Derivatives

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Myrtenal is a perspective monoterpenoid with therapeutic potential in various fields of medicine. Its chemical modifications often lead to new or more pronounced biological effects. As an example, the conjugation of myrtenal with the established pharmacophore adamantane enables the augmentation of several of its pivotal properties. Myrtenal–adamantane derivatives exhibited a variety of beneficial characteristics, such as antimicrobial, antifungal, antiviral, anticancer, anxiolytic, and neuroprotective properties, which are worth examining in more detail and at length.

Keywords: monoterpenes; pharmacophore; chemical modification; antiviral; anticancer; anxiolytic; neuroprotective activity

1. Introduction

Terpenes constitute the largest cluster of secondary plant metabolites, encompassing a plethora of over 50,000 distinct substances, each characterized by a diverse array of biological attributes. The most widespread terpenes are monoterpens consisting of two isoprene fragments. Monoterpenes that incorporate heteroatoms, such as oxygen, are categorized as monoterpenoids. As natural products, monoterpenes and monoterpenoids are the subject of increased attention from the world scientific community in the search for new pharmacological agents in various branches of medicine and pharmacy. They have many biological properties, including antifungal, antibacterial, antioxidant, anticancer, antispasmodic, hypotensive, vasodilating effects, etc.

A scarcity of substantiated data exists regarding the positive effects of monoterpene derivatives. Shi et al. (2016) reported on the antiallergic properties of some peony monoterpene derivatives. The review by Salakhutdinov, Volcho, and Yarovaya (2017) summarized the currently available data on the presence of various types of biological activity exhibited by monoterpenes and their derivatives. Their analgesic, anti-inflammatory, anticonvulsant, antidepressant, anti-Alzheimer’s, antiparkinsonian, antiviral, and antibacterial (antituberculosis) properties were described. In addition to these data, a compound synthesized by the interaction of (−)-myrtenal and 2-aminoadamatane was found to have anxiolytic activity in Elevated plus maze test in mice. In 2020, Zielińska-Błajet and Feder-Kubis provided a comprehensive summary of recent advancements in using derivatives of borneol, camphor, geraniol, myrtenal, pinene, and thymol as biologically active substances. In 2021, Silva et al. reviewed the potential of 16 monoterpenes and their derivatives to affect various models of cardiovascular disease. According to Bergman, Franks, and Philips (2023), certain acyclic monoterpenes and their derivatives have demonstrated notable anti-inflammatory potential. Several monoterpene–coumarin conjugates showed good antiviral activity, while others demonstrated the capacity to inhibit the enzyme TDP1, which serves as a pivotal target in the realm of anticancer therapy. The same inhibitory activity was demonstrated for some monoterpenes conjugated with various heterocyclic fragments. Cardoso et al. (2021) explored some monoterpenes derivatives as P-glycoprotein inhibitory activity agents in cancer cell resistance. Tree monoterpenes alkaloid hydrazone derivatives studied by Paterna et al. (2015) showed apoptosis-inducing properties in human colon and liver carcinoma cells.

Therefore, chemical modification of natural substances by conjugation with various synthetic components is a modern method for obtaining new biologically active compounds. It had been established that in many cases the medicinal properties of the obtained derivatives are more pronounced than those of the parent substances, and may even exceed the effects of the standards used in various therapeutic areas. It is necessary to carry out more in-depth and extended studies of such compounds. In view of their sufficient safety profiles, these compounds could subsequently be included in a range of clinical studies.

2. Therapeutic Potential of Myrtenal

(−)-Myrtenal, (1R)-2-pinen-10-al, (1R)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-carboxaldehyde (Figure 1), is a bicyclic monoterpenoid of natural origin.
Myrtenal is considered practically insoluble in water and relatively neutral. Data on its mammalian metabolism are limited. In plants, myrtenal is metabolically related to α-pinene because α-pinene is metabolized to myrtenol with subsequent transformation to myrtenal. The major metabolite of the monoterpenoid in rabbits is myrtenic acid. Furthermore, according to Scheline (1991), the structural similarity between alpha-pinene and myrtenal and the formation of common metabolites is the reason to assume that M is a transition compound in pinene metabolism.

Medicinal plants containing myrtenal in their essential oils possess a wide range of biological properties. In the 20th century, bronchodilator, anti-inflammatory, antiaggregative, antihemolytic (in vitro), and antibacterial (against G (+) pathogens) effects of myrtenal were discovered in experimental animals. This explains the use of plant essential oils containing myrtenal in aromatherapy for infections of the upper respiratory tract. They have the potential to favorably affect various systems and organs, including CNS functions, which is discussed in the review by Dragomanova et al. (2018).

2.1. Antidiabetic Potential

Myrtenal exhibited an antihyperglycemic effect in rats with an experimental streptozotocin-induced diabetes mellitus model. The compound lowered plasma glucose levels, improved plasma insulin levels, upregulated various glucose transporters, and subsequently improved glucose uptake in the liver and skeletal muscle. In the study by Rathinam and Pari (2016), oral administration of myrtenal (80 mg/kg b.wt.) for 28 days produced a number of effects in rats with induced diabetes. It reduced plasma glucose and glycated hemoglobin A1c (HbA1c); increased levels of insulin and hemoglobin; regained body weight; and normalized activity of hexokinase, glucose-6-phosphatase, fructose-1,6-bisphosphatase, glucose-6-phosphate dehydrogenase and liver enzymes AST, ALT, and ALP. Myrtenal also increased glycogen content in the liver and muscles; recovered the hepatocytes; and improved pancreatic insulin levels and lipid profile values (total cholesterol, triglycerides, phospholipids, low-density lipoprotein, very-low-density lipoprotein, atherogenic index) (Figure 2).

2.2. Antitumor Potential

Myrtenal has been shown to have antioxidant and antitumor activity in peroral administration at a dose of 230 mg/kg b.wt. in corn oil for 28 days. These effects were achieved through a variety of mechanisms of action, including stabilizing endogenous antioxidant protection, influencing apoptotic and proapoptotic signaling pathways, inhibiting the expression of...
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review articles, published in the last ten years

information regarding the biological and pharmacological properties of monoterpene derivatives remains limited to several

modifications of these natural compounds, including their biological effects and medical applications. However,

revealed the antiproliferative potential for two of them

structures

Zielińska-Błajet and Feder-Kubis (2020) provided an overview of diverse therapeutic effects on selected aliphatic,

3.1. Antitumor Potential

Pinene, whose derivative is M, showed analgesic potential in various models of induced pain [42]. On the other hand, the

hydroxyl derivative myrtenol suppressed nociceptive and inflammatory responses in experimental conditions by inhibiting

cell migration and neuromediation in pain pathways [43]. Intraperitoneal administration of this alcohol in experimental mice

reduced the number of spasms in the acetic acid writhing test. For the first time, a recent investigation demonstrated

myrtenal's analgesic potential in laboratory mice. After a single, 7-day, and 14-day i.p. administration (30 mg/kg), the

analgesic effect of M was established in two pain models: the acetic acid writhing test (antipyretic type analgesia) and the

hot plate test (narcotic-type analgesia) [45].

2.4. Anti-Inflammatory Potential

The anti-inflammatory activity of Myrtus communis, L. extracts was established in two chronic inflammation mice models:

a xylene-induced ear edema and a cotton pellet test [45]. In rats with induced rheumatoid arthritis, myrtenal isolated from

Liquidambra formosana L. exhibited anti-inflammatory properties [46]. They were manifested by lowering the plasma levels

of interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α), and also by suppressing the activation of the nucleotide-

binding, oligomerization domain (NOD)-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, which was

confirmed in vitro.

2.5. CNS-Affecting Potential

Subsequent research into the myrtenal effects on the CNS in experiments on laboratory rodents showed potentiation of

the classical sedative–hypnotic action of the drugs. These results are due to the interaction of myrtenal (20 and 30 mg/kg

i.p. in a single dose) with the GABA receptor, since the introduction of the benzodiazepine antagonist Flumazenil (0.5

mg/kg) is followed by a sharp recovery in the condition of the experimental animals [44]. The central mechanism for action

of myrtenal and its influence on GABA-ergic neurotransmission is related to the established anxiolytic properties of the

substance.

2.6. Neuroprotective Potential

The neuroprotective potential of myrtenal was investigated in an injury model in which experimental mice were exposed to

radiofrequency electromagnetic radiation during the gestational and neonatal periods. Akefe et al. (2023) administered

myrtenal orally at doses of 100 and 200 mg/kg for 28 days, observing improvement in memory processes and in some

biochemical parameters [47]. The substance improved short-term memory and spatial orientation. Additionally, it restored

the activity of antioxidant enzymes, thereby rectifying the oxidative–inflammatory status within the brains of the

experimental mice. The restoration of cholinergic neurotransmission and the levels of dopamine, noradrenaline, and

serotonin manifested myrtenal's neuromodulatory properties.

3. Therapeutic Potential of Myrtenal Derivatives

3.1. Antitumor Potential

Zielińska-Blajet and Feder-Kubis (2020) provided an overview of diverse therapeutic effects on selected aliphatic, mononuclear, and bicyclic monoterpenes such as geraniol, thymol, myrtenal, pinene, camphor, borneol, and their modified structures [42]. A recent study with fourteen newly synthesized perillaldehyde and myrtenal-based benzohydrazides revealed the antiproliferative potential for two of them [48]. Increasingly more literature data are available regarding new modifications of these natural compounds, including their biological effects and medical applications. However, information regarding the biological and pharmacological properties of monoterpenic derivatives remains limited to several review articles, published in the last ten years [49].

Gonda and Szakonyi (2018) reported the synthesis of 1,2,4- and 1,3,4-oxadiazole derivatives of (–)-myrtenal [50]. All compounds were tested in vitro for antiproliferative activity against four human malignant cell lines using the MTT [3-(4,5-
dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. One of them inhibited tumor growth, with IC50 values comparable to those of the reference cisplatin, but showed lower antiproliferative activity against the triple-negative breast cancer cell line (MDA-MB-231) compared to other cell lines used in gynecology. The remaining compounds exhibited a relatively diminished level of activity against ovarian cancer (cell line A2780).

3.2. Anxiolytic Potential

Kapitsa et al. (2012) described new nitrogen-containing compounds with an adamantane–myrtenal structure and then investigated the anxiolytic activity of the resulting products in male Balb/C mice by using the elevated plus maze test.

3.3. Antiviral Potential

Teplov et al. (2013) tested in vitro the same conjugate of 2-amino adamantane and (−)-myrtenal for antiviral activity against influenza virus A/California/07/09 (H1N1)pdm09 and found that the introduction of a myrtenal fragment led to an increase in the antiviral activity of the adamantylamine derivatives against the adamantylamine-resistant virus. The selectivity for most of the synthesized amines surpassed that for Rimantadine and Amantadine.

3.4. Antifungal Potential

Compound 10, which is a myrtenol-containing analogue of azole antifungals, demonstrated promising antifungal activity against both fluconazole-susceptible and fluconazole-resistant strains, including fluconazole-resistant clinical isolates of Candida parapsilosis and Candida glabrata, with excellent minimum inhibitory concentration in submicrogram and nanogram range. The compound was up to 100 times more active than fluconazole.

3.5. Analgesic Potential

A high analgesic effect with an active dose of 20 mg/kg was shown for myrtenal-derived diazaadamantanone. The compound has a low acute oral toxicity with LD50 of more than 1000 mg/kg and does not cause damage to the gastric mucosa. Similar analgesic activity was demonstrated for diazaadamantanone–myrtenal conjugate. Having in mind evidences for analgesic potential of myrtenal established in previous studies, it can be concluded that this analgesic potential can be improved and extended via synthesis of some diazaadamantanone analogues of myrtenal.

3.6. Memory-Improving Potential

The conjugates of amino adamantane with myrtenal, in the form of hydrochlorides, studied by Kapitsa (2012) and Teplov (2013), showed the potential to influence memory processes in intact rats after 11 days of repeated intraperitoneal administration at a dose of 1 mg/kg. The two compounds of amino adamantane with myrtenal investigated in this study exhibited antiacetylcholinesterase activity. Additionally, they demonstrated the capability to influence the levels of norepinephrine and serotonin in the cerebral cortex and hippocampus of the experimental animals. Notably, one of these substances also displayed antidepressant potential, which can be attributed to the induced increase in brain monoamines concentrations, the reduced levels of which are associated with depressive conditions.

4. Conclusions

As a natural compound with a wide range in biological activities, myrtenal can have future implementation in medical practice. The chemical modification of this monoterpenoid with some pharmacophores will allow the enhancement of its essential properties, thereby augmenting its therapeutic potential.

References


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