Review

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Posted Date: 30 August 2023

doi: 10.20944/preprints202308.2076.v1

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Therapeutic Potential of Myrtenal and Its Derivatives–A Review

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Abstract: Monoterpenes as natural products are the subject of increased attention in the search for new pharmacological agents because of their numerous biological activities including antifungal, antibacterial, antioxidant, anticancer, antispasmodic, hypotensive, vasodilating effects, etc. In vitro and in vivo studies reveal their antidepressant, anxiolytic, and memory-enhancing in experimental dementia and Parkinson's disease effects. Chemical modification of natural substances by conjugation with various synthetic components is a modern method of obtaining new biologically active compounds. The discovery of new potential drugs among monoterpene derivatives is a progressive direction in experimental pharmacology and a promising approach to the therapy of various pathologies. Biologically active substances such as monoterpenes borneol, camphor, geraniol, pinene, and thymol, were used to synthesize compounds with different properties, including analgesic, anti-inflammatory, anticonvulsant, anti-depressant, anti-Alzheimer's, anti-parkinsonian, antiviral and antibacterial (anti-tuberculosis). 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, conjugation of myrtenal with the known pharmacophore adamantane allows one to enhance some of its key properties. Myrtenal-adamantane derivatives exhibited a variety of beneficial properties – antimicrobial, antifungal, antiviral, anticancer, anxiolytic, and neuroprotective, which are worth examining in more detail and at length.

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

1. Introduction

Essential oils have been used in folk medicine to treat different diseases, as well as perfumes and fragrances for many years before their research began. Some of their components have rich biological activity [1–7] and are used as pharmacological agents such as taxanes with antitumor activity and artemisinin with antimalarial properties [8,9]. Natural products and their derivatives dominate among drugs for CNS diseases [10–13].

Terpenes are the largest group of secondary plant metabolites, represented by more than 50,000 substances, which are characterized by a variety of biological properties [14]. The most widespread terpenes are monoterpenes consisting of two isoprene fragments [15]. Monoterpenes containing heteroatoms such as oxygen are called monoterpenoids. Monoterpenes and monoterpenoids as natural products 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 [16–26]. They

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have many biological activities, including antifungal, antibacterial, antioxidant, anticancer, antispasmodic, hypotensive, vasodilating effects, etc. The review by Yang et al. (2020) on the biological properties of terpenoids addresses the topic of their therapeutic potential and confirms the interest of researchers in developing their derivatives with different pharmacological properties [27]. Recently, another paper from 2022 (Kumar et al.) summarized the current data about the therapeutic potential of terpenes and terpenoids, confirming that these natural substances are widely distributed in various plant and marine sources and possess a wide range of biological properties [28].

In vitro and in vivo studies reveal their potential therapeutic effects on diabetes, insulin resistance, and obesity, as described by Habtemariam (2017) [29] and Al Kury et al. (2021) [30]. Genipin and geniposide (Figure 1), as well as iridoids and their glycosides, exhibit in vitro antidiabetic properties. Geniposide stimulates insulin secretion by activating the glucagon-like-1 (GLP-1) receptor [31]. Limonene showed a promising in vivo antidiabetic effect, established by Ramakrishnan and Ramalingam in 2012 [32]. Borneol, citronellol, and myrtenal increased liver glycogen levels. Carvacrol, carvone, citronellol, genposide, myrtenal, and paeoniflorin modulated key liver enzymes of glucose metabolism, reducing the activity of glucokinase and glucose-6-phosphate dehydrogenase.

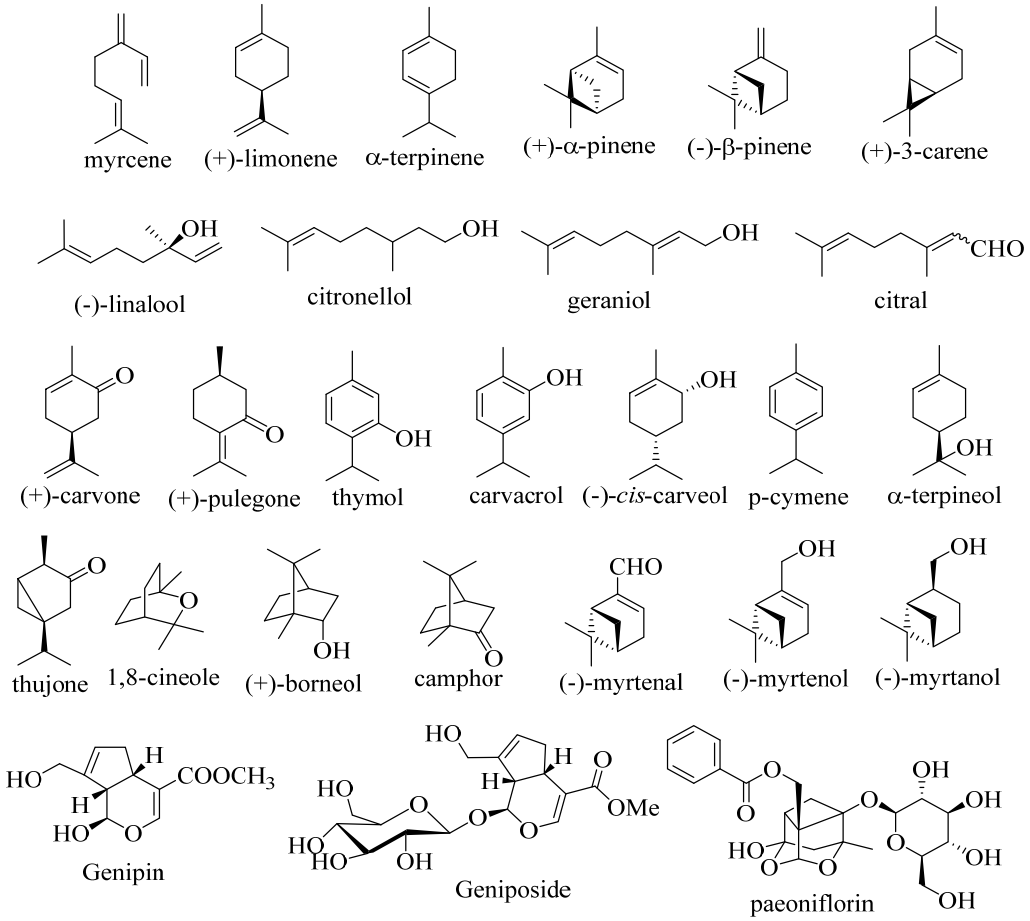

Figure 1. Some bioactive monoterpenes and monoterpenoids.

In 2013, Luft et al. in a clinical study proved the role of chronic inflammation in the pathogenesis of diabetes and obesity [33]. Many of the monoterpenes exhibit positive effects in inflammatory conditions [34], also associated with diabetes. The in vitro study by Kong et al. (2013) reported that they directly improve the lipid profile by affecting key enzymes for fatty acid synthesis (acetyl-CoA carboxylase and synthase) [35]. De Sousa (2011) summarized the available data about the analgesic potential of many plant essential oils rich in monoterpenes [36]. Numerous works have been carried out in this important field in the last decade. Thus, high analgesic activity was demonstrated for (−)-

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linalool [37] and its acetate [38], citronellal [39], p-cymene [40,41], camphor [42], α-terpineol [43–46], menthol [47], myrcene [48], limonene [49,50], pulegone [51], citronellol [52], cuminic alcohol [53], and 1,8-cineole [54]. The anti-inflammatory activity of monoterpenes was reviewed by Araruna et al. (2020) [55].

In some representatives, positive effects were observed as an adjunct to radiation therapy in cancer. They have the potential of "radiosensitizers" increasing the in vitro sensitivity of cancer cells (head and neck tumors) to radiation therapy with subsequent induction of apoptosis [56]. In addition to studies on their cytotoxic properties as potential antitumor agents, studies on their toxicity and potential risk of use are also of interest. Wojtunik-Kulesza K. (2022) revealed the toxic potential of α-terpinene, camphor, citral, limonene, pulegone, thujone (Figure 1), and the essential oils that contain them [57]. Genotoxicity, embryotoxicity, neurotoxicity, and allergenicity were indicated.

Memory-enhancing properties have also been reported for some of the monoterpenes studied [58]. Such an example is thymol's positive effect on cognitive deficits, associated with a high-fat diet in mice found by Fang et al. (2017) [59]. According to Deng, Lu, and Teng (2013), carvacrol counteracted rats' memory impairments associated with experimental diabetes by affecting different mechanisms [60]. Some of the bicyclic monoterpenoids inhibit acetylcholinesterase activity, which is elevated in Alzheimer's disease patients. In Miyazawa and Yamafuji's (2005) study of 17 representatives of this group of substances, (+)- and (-)-α-pinene, and (+)-3-carene (Figure 1) appeared as moderate inhibitors of the enzyme, while bicyclic ketones and alcohols are weak anticholinesterase agents [61]. Their oxygenated derivatives and para-menthane monoterpenoids were found to be even less active.

A number of monoterpenoid alcohols including geraniol [62,63], diol 1 derived from verbenol [64], and a conjugate 2 obtained by reaction of (+)-2-carene with vanillin [65] demonstrated promising anti-parkinsonian activity in vivo in MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mouse model. Derivatives of diol 1, compounds 3 and 4, showed neuroprotective effects in vitro and in several experimental mice models (MPTP-, rotenone- and haloperidol-induced) of Parkinson's disease [66,67] (Figure 2). Neuroprotective potential was demonstrated also for carvacrol [68–70], limonene [71–73], geraniol [74,75], citronellol [76], carveol [77], 1,8-cineole [78], paeoniflorin [79], α-pinene [80], and linalool [81].

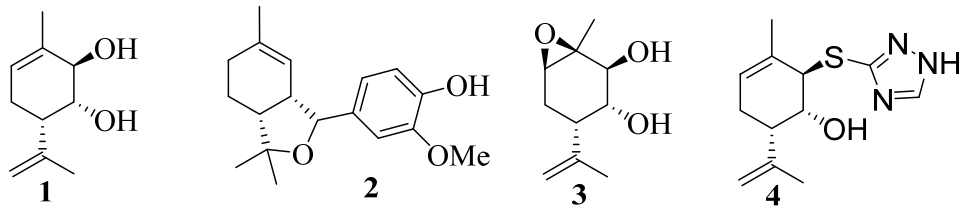

Figure 2. Some monoterpenoids with anti-parkinsonian activity (*1-4*).

Guzmán-Gutiérrez et al. (2012) reported the antidepressant effect of β-pinene and linalool [82], and Deng et al. (2015) found that thymol demonstrated such properties in a model of chronic mild stress in mice [83]. A number of monoterpenoids have demonstrated anxiolytic effects in rodents [84]. In 2015, de Sousa et al. published a systematic review of the anxiolytic-like effect of essential oils and their components, mainly monoterpenoids.

The discovery of new potential drugs among monoterpene derivatives is a progressive direction in experimental pharmacology and a promising approach to the therapy of various pathologies.

2. Therapeutic potential of monoterpenoid derivatives

Information regarding the established positive effects of monoterpene derivatives is scarce. Shi et al. (2016) reported about the anti-allergic properties of some peony monoterpenes derivatives [85]. 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, including analgesic, anti-inflammatory, anticonvulsant, anti-depressant, anti-

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Alzheimer's, anti-parkinsonian, antiviral and antibacterial (anti-tuberculosis) effects [86]. In addition to these data, a compound synthesized by the interaction of (-)-myrtenal and 2-aminoadamatane was found to have anxiolytic activity in mice using the elevated plus maze test [87]. In 2020 Zielińska-Błajet and Feder-Kubis summarized the recent development of the derivatives of borneol, camphor, geraniol, myrtenal, pinene, and thymol as biologically active substances. Silva et al. reviewed the potential of 16 monoterpenes and their derivatives to affect various models of cardiovascular disease in 2021 [88]. Some acyclic monoterpenes and their derivatives showed anti-herbivory and anti-inflammatory potential according to Bergman, Franks, and Phillips (2023) [89]. Several monoterpene-coumarin conjugates showed good antiviral activity [90,91], while others demonstrated the ability to inhibit enzyme TDP1, an important target for anticancer therapy [92,93]. The same inhibitory activity was demonstrated for some monoterpenes conjugated with various heterocyclic fragments [94,95]. Some monoterpene derivatives were explored as P-glycoprotein inhibitory activity in cancer cell resistance by Cardoso et al. (2021) [96]. Tree monoterpene alkaloid hydrazone derivatives from the study of Paterna et al. (2015) showed apoptosis-inducing properties in human colon and liver carcinoma cells [97].

Thus, chemical modification of natural substances by conjugation with various synthetic components is a modern method of obtaining new biologically active compounds. It has 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.

3. Therapeutic potential of myrtenal

(−)-Myrtenal, (1*R*)-2-pinen-10-al, (1*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-carboxaldehyde (Figure 3), is a bicyclic monoterpenoid of natural origin.

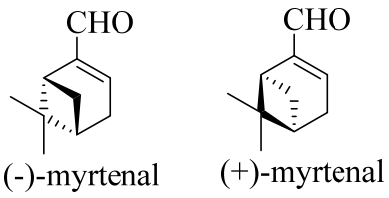

Figure 3. Structure of Myrtenal.

The substance is a component of the essential oils of many plant species (Dragomanova et al., 2018). It is naturally present in mandarin peel oil, raspberry, blackberry, strawberry, ginger, hop oil, black tea, peppermint oil, pepper, myrtle leaf or berry, summer savory and other spices or foodstuffs including hyssops, rosemary, spearmint, and many more. Table 1 presents the sources with the highest myrtenal content in their essential oils.

Table 1. Myrtenal-containing medicinal plants and other natural sources

Natural source	*Reference*
Artemisia spp.	[98]
Coriandrum sativum	[99]
Cuminum cyminum	[100,101]
Curcuma amada, Curcuma aromatica	[102]
Glycyrrhyza glabra	[103]

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Helianthus annuus	[104]
Hyssopus officinalis	[105]
Juglans regia	[106]
Laurus nobilis	[103]
Lavandula spp.	[107]
Ledum palustre	[108]
Myrtus communis	[109]
Origanum majorana, Origanum vulgare	[110]
Peumus boldus	[103]
Piper nigrum	[103]
Propolis	[111]
Rosmarinus officinalis	[112]
Thymus spp.	[113]

Medicinal plants containing myrtenal in their essential oils possess a wide range of biological properties In the 20th century, multiple effects of myrtenal were discovered on experimental animals – bronchodilator, anti-inflammatory, anti-aggregative, and anti-hemolytic (in vitro), and antibacterial (against G (+) pathogens) [114]. This explains the use of plant essential oils containing myrtenal in aromatherapy for upper respiratory tract infections. 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) [115]. According to Saito et al. (1996) [116] and Santos et al. (2011) [117] the compound induced vasodilation, decreased heart rate, and hypotension in doses 1 and 5 mg/kg b.wt. after i.v. application in laboratory rats.

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) [118], oral administration of myrtenal (80 mg/kg b. wt.) for 28 days produced a number of effects in rats with induced diabetes – reduced plasma glucose and glycated hemoglobin A1c (HbA1c); increased levels of insulin and hemoglobin; regained body weight; normalized activity of hexokinase, glucose-6-phosphatase, fructose-1,6-bisphosphatase, glucose-6-phosphate dehydrogenase and liver enzymes AST, ALT, and ALP; increased glycogen content in the liver and muscles; recovered the hepatocytes; improved pancreatic insulin levels and lipid profile (total cholesterol, triglycerides, phospholipids, low-density lipoprotein, very-low-density lipoprotein, atherogenic index).

Antioxidant and antitumor activity of myrtenal (oral administration at a dose of 230 mg/kg b.wt. in corn oil for 28 days) have also been reported, carried out by different mechanisms of action – influencing apoptotic and proapoptotic signaling pathways, stabilizing endogenous antioxidant protection, suppressing the expression of TNF-α and suppressing tumor growth, regulating the activity of a number of lysosomal and mitochondrial enzymes influencing the processes of gluconeogenesis in tumor cells [119–122]. The monoterpenoid was administered for 28 days in the experimental protocols of Babu et al., and Venkatachalam's research group applied it for 15 weeks. Myrtenal was found to inhibit V-type ATPase on the surface of tumor cells in an in vitro study in

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melanoma cell lines, leading to their death and also to the suppression of melanoma metastasis in experimental mice at a dose of 15 mg/kg b. wt. (i.p. application for 21 days) [123]. In the in vivo studies of Lokeshkumar et al. from 2015 and 2016 [124,125], the monoterpenoid exhibited the ability to inactivate free radicals with subsequent inhibition of colon carcinogenesis in Wistar rats and suppression of tumor progression after 30 weeks of intragastric administration at a dose of 230 mg/kg b. wt. Trytek et al. (2018) investigated the antitumor potential of (−)-myrtenol (Figure 1), (−)-myrtanol, and (−)-myrtenal on human colon carcinoma cells in vitro and found that myrtenal had the highest activity [126]. The mechanism of antitumor action proposed was affecting the mitochondrial enzymes' activity and membrane stability. Our results confirmed the antioxidant mechanisms in the CNS effect of myrtenal (40 mg/kg b. wt. applied intraperitoneally for 11 days) in intact rats, in the brain of which myrtenal caused SOD (superoxide dismutase) activity and malondialdehyde (MDA) levels decrease, as well as total glutathione (tGSH) content increase in compared to controls [127].

Our recent investigation demonstrated for the first time myrtenal's analgesic potential in laboratory mice. The effect was established in two pain models after single, 7-day, and 14-day i.p. administration (30 mg/kg) – Acetic acid writhing test (antipyretic type analgesia) and Hot plate test (narcotic type analgesia) [128]. The subsequent research of myrtenal effects on the CNS in laboratory rodents showed potentiation of the classical sedative-hypnotic drugs' action. In our opinion, 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 of the condition of the experimental animals [129]. The central mechanism of action of myrtenal and its influence on GABA-ergic neurotransmission is related to the established anxiolytic properties of the substance. Hailu et al. (2011) reported good anxiolytic effects of myrtle essential oil comparable to those of diazepam [130]. Our studies in mice confirmed the anxiolytic property of myrtenal according to the Marble-burying test after single and repeated 7- and 14-day i.p. administration at 30 mg/kg dose, comparable to that of diazepam (1 mg/kg) as a reference [129].

For the first time, our team demonstrated the ability of natural myrtenal to affect neurodegenerative diseases. In two experimental models of neurodegeneration – 6-OHDA-induced parkinsonism [131] and chemically induced dementia [132] in rats, we have established, the antioxidant potential of the compound (50 mg/kg i.p. for 5 days), as an element of its neuroprotective activity. There is limited data in the literature on myrtenal effects on the major brain neurotransmitters levels. The reported by Kaufmann, Dogra, and Wink (2011) [133] in vitro anti-cholinesterase effects were not confirmed by the presence of direct inhibition of enzyme activity in our in vivo experiments in mice (20 mg/kg, i.p. for 11 days) [134] and rats (40 mg/kg, i.p. for 9 days) with experimental neurodegeneration [132]. We established a significant protective effect of myrtenal on neurodegenerative processes in experimental rodent models [129]. Under the conditions of our studies in a scopolamine injury model of dementia, the monoterpenoid exhibited neuromodulatory properties through a slight non-significant decrease in brain AChE activity, a significant decrease in hippocampal noradrenaline content, and increased hippocampal and cortical serotonin levels in experimental rats. Examining the myrtenal (50 mg/kg i.p. for 5 days) neuroprotective effects on an experimental 6-OHDA model of Parkinson's disease further revealed the multitarget mechanism of its action. It demonstrated positive effects on the memory and learning abilities, on the coordination and exploratory behavior of experimental rats, via reducing the main parameters of brain oxidative stress, and increasing the dopamine content in the damaged cerebral hemisphere [131]. According to our studies, at least two mechanisms were involved in the protective effects of myrtenal on neurodegenerative processes – neuromodulatory and antioxidant.

There is only one pharmaceutical product based on natural myrtenal. Myrtecaine is with local anesthetic activity. Its combination with diethyl amine and salicylic acid is used for muscle and joint pain topical treatment.

4. Therapeutic potential of myrtenal derivatives

Monoterpenes and their derivatives are key starting components in the design and synthesis of new biologically active compounds.

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Concepción et al. (2020) described several basic structures of myrtenal conjugates such as compound **5** (Figure 3) with high cytotoxicity against cancer cells with EC_{50} in the nanomolar range [135]. These novel myrtenal-conjugated pseudo-peptides have been synthesized and investigated as possible antitumor agents as new potential anticancer candidates with selective cytotoxic activity. Some of these compounds showed significant cytotoxicity in vitro against human gastric, breast, and colon adenocarcinoma cell lines, but not against human dermal fibroblast cell lines. One derivative exhibited acceptable EC_{50} and Emax values in cancer cell lines and in inducing cytotoxicity in actively proliferating CD4+ - T cells without affecting non-proliferating T cells.

Zielińska-Błajet and Feder-Kubis (2020) provided an overview of diverse therapeutic effects on selected aliphatic, monocyclic, and bicyclic monoterpenes such as geraniol, thymol, myrtenal, pinene, camphor, borneol, and their modified structures [136]. A recent study with fourteen newly synthesized substances revealed the anti-proliferative potential of two myrtenal-based structures [137]. More and more literature data are available regarding new modifications of these natural compounds, including their biological effects and medicinal applications. However, information on the biological and pharmacological properties of monoterpene derivatives remains limited in several review articles for the last ten years [89,115,138–144].

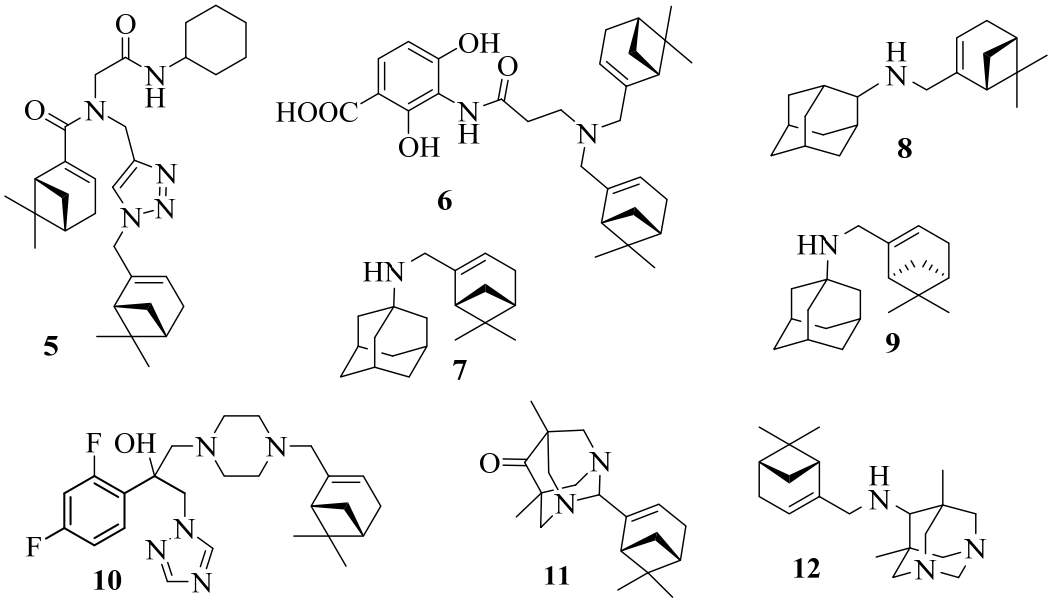

Figure 4. Structures of biologically active myrtenal-derived compounds (**5 – 12**).

In 2011, Wang and Sintim developed compound **6** (Figure 3), myrtenal analogs of two natural antibiotics (platensimycin and platencina), with promising antibacterial activity with MIC 4 μ/mL [145].

In 2015, Suslov et al. published that amino adamantane derivatives of myrtenal **7** and **8** possess potent cytotoxic effects against tumor lines used (CTD_{50} = 12÷21 μM) along with low toxicity with respect to MDCK cells [146]. Compound **7**, which was synthesized from 1-amino adamantane and (–)-myrtenal, showed cytotoxic activity against CEM-13, MT-4, and U-937 human cancer cells. Adamantylamine derivative demonstrated high activity against all tumor lines used, along with low cellular toxicity, while the 1-amino adamantane and (+)-myrtenal derived compound **9** exhibited antitumor potential by inhibiting tyrosyl-DNA phosphodiesterase 1 activity, an important target for antitumor therapy, according to the research of Ponomarev et al. (2018) [147]. Moreover, these myrtenal derivatives do not exert genotoxic properties.

Gonda and Szakonyi (2018) reported the synthesis of 1,2,4- and 1,3,4-oxadiazole derivatives of (–)-myrtenal [148]. 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 [149]. One of them inhibited tumor growth, with IC_{50} values comparable to those of

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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 showed weaker activity against ovarian cancer (cell line (A2780)).

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 with the elevated plus maze test [150]. The results showed that compound **8** exhibited anxiolytic potential upon single administration.

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 [151]. The selectivity of most of the synthesized amines was higher than that of Rimantadine and Amantadine.

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 [152].

A high analgesic effect with an active dose of 20 mg/kg was shown for myrtenal-derived diazaadamantanone **11** [153]. The compound has a low acute toxicity with LD_{50} of more than 1000 mg/kg and does not cause damage to the gastric mucosa. Similar analgesic activity was demonstrated for another diazaadamantane-myrtenal conjugate **12** [154]. The conjugates of amino adamantane with myrtenal **7** and **8**, studied by Kapitsa (2012) [150] and Teplov (2013) [151], showed, in the form of hydrochlorides, the potential to influence memory processes in intact rats after 11 days of repeated intraperitoneal administration in a dose of 1 mg/kg [155]. The two compounds of amino adamantane with myrtenal investigated in this study demonstrated anti-acetylcholinesterase activity as well as the property to affect the content of norepinephrine and serotonin in the cerebral cortex and hippocampus of the experimental animals. One of the substances showed antidepressant potential related to the induced increase in the brain monoamines concentrations, the reduced levels of which are associated with depressive states.

The study of these two compounds of amino adamantane with myrtenal was extended by examining their effects on scopolamine-induced neurodegeneration in rats [156]. The derivatives again caused AChE activity inhibition in the cerebral cortex of demented rats, accompanied by some antioxidant capacity expressed by increased glutathione content. They also affected the levels of norepinephrine and serotonin in the cortex and hippocampus of laboratory rodents with an induced model of dementia, as was observed in intact rats in the previous study. These studies reveal for the first time the property of the two conjugates of amino adamantane with myrtenal to affect neurodegenerative processes by different mechanisms of action – anti-acetylcholinesterase and neuromodulatory.

5. Conclusions and future perspectives

As a natural compound with a wide range of biological activities, Myrtenal can have perspective implementation in medical practice. The chemical modification of this monoterpenoid with the known pharmacophore adamantane will allow the enhancement of some of its key properties and improve its therapeutic potential. Different combinations of myrtenal and adamantane moieties have gained interest in various fields, including medicinal chemistry and drug discovery. Some research focuses on the design, synthesis, and evaluation of myrtenal-adamantane conjugates as potential pharmacological agents. Moreover, other analogs of these conjugates with modification of monoterpene, adamantine, and linker structures could be considered in the future. Several possible areas of applications of these derivatives include antimicrobial, antifungal and antiviral, anticancer, anxiolytic, and neuroprotective activity. This group of compounds exhibited a variety of beneficial properties that are worth examining in more detail and at length. They have the potential to be introduced in the future into various areas of pharmacotherapeutic practice.

Author Contributions: Conceptualization, S.D., K.V., and L.T.; investigation, S.D., K.V.; writing—original draft preparation, S.D., K.V.; writing—review and editing, L.T., R.K., N.S., K.V., V.A.; visualization, K.V., S.D.; supervision, L.T., R.K., N.S., K.V., V.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.
Conflicts of Interest: The authors declare no conflict of interest.

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