

Is Myrto[®] Standardized a New Alternative toward Antibiotics?

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ABSTRACT

GeloMyrto[®] and GeloMyrto[®] forte, also known as Myrto[®] standardized, is an herbal medical product (phytomedicine) obtained by a multistep distillation procedure from essential oils. The major biological marker of *in vivo* and *ex vivo* activity of Myrto[®] standardized is the monoterpenes, d-limonene, 1,8-cineole, and alpha-pinene. Myrto[®] standardized is estimated to have antioxidative, anti-inflammatory, and antibacterial potential while many studies confirmed its secretolytic and bronchospasmodic effects. As such, the medication is proposed to be initiated in several acute and chronic infections of the upper and lower airway system as acute and chronic rhinosinusitis, acute and chronic bronchitis, and chronic obstructive pulmonary disease. This review intends to give an insight into several prescription indications of Myrto[®] standardized, all involved mechanisms, and potential advantages toward antibiotic therapy, especially in cases when bacterial infection is uncertain.

Key words: Antibiotics, GeloMyrto[®], GeloMyrto[®] forte, indications, mechanisms, Myrto[®] standardized

INTRODUCTION

GeloMyrto[®] and GeloMyrto[®] forte, also known in the literature as Myrto[®] standardized, is an herbal medical product (phytomedicine) obtained by a multistep distillation procedure from essential oils. The major biological substances of *in vivo* and *in vitro* activity of Myrto[®] standardized are the monoterpenes, d-limonene, 1,8-cineole, and alpha-pinene.^[1] According to many *in vivo* and *ex vivo* studies, Myrto[®] standardized is estimated to have a significant secretolytic and secretomotoric effects, leading to increase of upper and lower airway patency and subsequently to rapid relief of patients' symptoms.^[1-3] Due to its additional antioxidative, anti-inflammatory and antibacterial potential, the medication has been implemented therapeutically in several acute and chronic infections of the upper and lower airway system, such as acute and chronic rhinosinusitis, acute and chronic bronchitis and chronic obstructive pulmonary disease (COPD).^[4,5] The medication has been implemented therapeutically in several acute and chronic infections of the upper and lower airway system, such as acute and chronic rhinosinusitis, acute and chronic bronchitis, and chronic obstructive pulmonary disease (COPD). This review gives an insight into the already proposed indications of Myrto[®] standardized, involved pharmacodynamic mechanisms, and potential advantages toward antibiotic therapy, especially when bacterial infection is uncertain.

MATERIALS AND METHODS

Literature research was conducted in PubMed Database using the MeSH Terms: "GeloMyrto[®]," "GeloMyrto[®] forte," and "Myrto[®] standardized."

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Further, documented publications provided by manufacture's database were included.

RESULTS AND DISCUSSION

Pharmacodynamics

Secretolytic and secretomotoric effects

The first study to date the secretolytic and secretomotoric effects of GeloMyrto[®] forte was performed *in vivo* in healthy volunteers and published on 1995 from Behrbohm *et al.*^[2] According to the protocol, 0.2 ml of NaCl solution enriched with radioactive 99 m technetium-sulphur colloid was injected into the maxillary sinus of the study participants, and the mucociliary transport velocity was measured as the accumulation of radioactivity in a tampon placed in the middle meatus of the nose. The mucociliary transport velocity was clearly increased after intake of secretolytics.

Similar *in vivo* effect of Myrto[®] standardized was shown by Han *et al.*,^[3] who measured the mucociliary transport time (MTT) by acoustic rhinometry and active anterior rhinomanometry in patients with chronic nonallergic rhinitis after implementing saccharine test. Except of MTT further parameters of nasal patency, such as unilateral minimum cross-sectional area, volume inside the nasal cavity, unilateral nasal resistance, and total symptom visual analog score were also evaluated during this study. The increase of nasal patency was a significant indicator of rapid subjective symptom relief. According to this study, there was no impact on ciliary beat frequency (CBF) of *ex vivo* cultured nasal cells under immediate or prolonged treatment with Myrto[®] standardized.

However, a future study by Begrow *et al.*^[1] shown that the CBF can be indeed accelerated *in vivo* under treatment with Myrto[®] standardized. CBF was measured in rat tracheal explants using the method of high-speed video microscopy, and it was increased in a concentration-dependent

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manner. Extremely high doses of Myrtol were, however, not able to additionally increase the CBF effect in comparison to salbutamol.

Antioxidative and anti-inflammatory effects

Pathogenesis and symptoms of many acute or chronic inflammatory processes are accompanied and/or initiated by the production of reactive oxygen species (ROS). Environmental factors (gases, air particles, and allergic agents) or infectious agents can lead to leukocyte activation and subsequently production of aggressive oxygen radicals of OH⁻ type. These oxygen radicals are able to cause severe damage to alveolar epithelial cells, described under the definition of "oxidative stress."^[6] The effect of essential oils on the production of ROS was studied by Grassmann *et al.* with the aid of biochemical model reactions simulating several *in vivo* pathological events.^[4] It was shown that Myrtol[®] standardized and eucalyptus oil can ameliorate the inflammatory processes by interfering to the leukocyte activation. These properties allow the inhibition of oxidative stress, and the attenuation of subsequent damage induced by infections or environmental impacts.

Except of its antioxidative properties Myrtol[®] standardized (GeloMyrtol[®]/GeloMyrtol[®] forte) can have an anti-inflammatory effect, by the inhibition of cytokine production. Beuscher *et al.*^[5] shown that the oral application of Myrtol[®] standardized significantly reduced the formation of leukotriene C4/D4/E4 based on the Opas *et al.*^[7] research model (a topical inflammatory reaction is caused after local application of arachidonic acid on the skin of mouse ears, and leukotriene C4/D4/E4 is measured in the ear skin several hours after initiation of inflammation). This means that Myrtol[®] standardized can act bronchospasmolytic as leukotriene C4/D4 and E4 have a confirmed bronchoconstrictive activity.^[8]

Furthermore, the experimentally proven inhibition of the enzyme 5-lipoxygenase in leukemic basophil and eosinophil leukocytes of rats and the production of prostaglandin E2 in mucous membranes of teat cisterns after topical administration of TPA (tetradecanoylphorbol-13-acetate) indicate a wide range of anti-inflammatory potential by blocking many different inflammatory pathways.

After local administration into the teat cisterns of the isolated bovine udder, Myrtol[®] standardized increased the surface temperature, similarly to menthol, which can be an indicator of vasodilatation properties.^[4]

Pharmacokinetics

An open, randomized cross-over trial was performed by Zimmermann *et al.*^[9] to evaluate the relative bioavailability and the pharmacokinetics of Myrtol[®] standardized, the active ingredient of GeloMyrtol[®] and GeloMyrtol[®] forte capsules. Twenty healthy volunteers were given 1 capsule of GeloMyrtol[®] (120 mg myrtol stand.) crushed and uncrushed and 1 capsule of GeloMyrtol[®] forte (300 mg myrtol stand.) crushed and uncrushed in a randomized way on four different days with an interval of 6 days without any therapy. The medication had to be taken always at about 8 a.m. with 200 ml of water. Peripheral blood samples were collected prior and several minutes till 24 h after medication application. According to the results of the study, cineole which is the main active component of Myrtol[®] standardized, was absorbed to 93.2% from GeloMyrtol[®] capsules and 95.6% from GeloMyrtol[®] forte capsules, compared to the liquid form of administration (crushed capsule). The enteric coating of the capsules prevents against rapid absorption of the medication and subsequently high peak plasma concentrations and results to a plateau-like phase of plasma concentrations only a few hours after application, which should be considered as an important therapeutic advantage of the enteric coating.

However, there is one case reported in the literature, where anaphylactic shock was developed after receiving a GeloMyrtol[®] forte capsule to

treat an upper respiratory system infection.^[10] Itching, urticaria, and respiratory distress syndrome occurred 20 min after application of the medication, and prick tests were highly positive for the substance dibutyl phthalate, which is a plasticizer of capsule coating.

Prescription indications

Acute rhinosinusitis

Acute rhinosinusitis (ARS) is a very common infection of the upper airway system and one of the most common causes of general practitioner visits worldwide. The majority of patients seek medical care within the 1st week of the disease course to be relieved from the severity of their symptoms.^[11] Still, very high rates of antibiotics are prescribed, that are considerably in excess of what is clinically justified.^[12] For instance, in ARS, the incidence of bacterial infections is estimated to be only 2–10%, with a secondary bacterial infection occurring only in 0.5–2% of the adult cases.^[13] In this context, Myrtol[®] standardized was evaluated as a therapeutic alternative, especially in patients where bacterial infection is uncertain.

Federspil *et al.* tested in a multicenter, randomized, double-blinded study, the efficacy and safety of Myrtol[®] standardized in patients with nonpurulent acute sinusitis, in comparison to placebo and other etheric oil with similar pharmacological activity.^[14] All study participants were treated for 6 ± 2 days with the respective study medication (GeloMyrtol[®] forte or placebo or essential oil) and then evaluated in terms of efficacy and tolerance at the end of the observational period of 14 days. Regarding the efficacy, both GeloMyrtol[®] forte and the essential oil proved to be significantly superior to placebo while GeloMyrtol[®] forte demonstrated a slight advantage of tolerance in comparison to the other essential oil.

This was the first systematically conducted study to demonstrate the importance of the maintenance of permanent ventilation and drainage of the sinuses as a therapeutic concept in acute, uncomplicated sinusitis, instead of antibiotics as a first choice.^[15] The antibiotic therapy should be strictly restricted to purulent forms because of the rapid increase of antibiotic resistance.

Chronic sinusitis

De Mey and Riechelmann conducted a multicenter, randomized, double-blind, placebo-controlled clinical trial where Myrtol[®] standardized (GeloMyrtol[®] forte) was tested against placebo in patients with chronic sinusitis for a time period of 3 months.^[16] The study involved 48 patients with evidence of chronic sinusitis based on the Lund-Mackay score in the computer tomography of the sinuses.^[17] The Lund-Mackay score was used as an objective criterion of selection and evaluation of the study participants because clinical symptoms in chronic sinusitis can be missed or occurring sporadically. The study subjects received Myrtol[®] standardized 3 × 300 mg/day or placebo for 3 months. Patients with anatomical sinus abnormalities, nasal polyposis or former operations in the region of sinuses, bronchial asthma, or cortisone therapy were excluded. After 3 months of treatment, the group under GeloMyrtol[®] forte showed a significant lower Lund-Mackay score in the control-computer tomography of the sinuses comparing to the placebo group, where radiological findings were unchanged.

Acute bronchitis

Matthys *et al.* conducted a multicenter, randomized, double-blind, placebo-controlled clinical trial comparing the efficacy, tolerability, and safety of a 2-week treatment (4 × 300 mg, day 1–14), with Myrtol[®] standardized versus placebo or cefuroxime or ambroxol in patients with acute bronchitis of recent onset, without evidence or suspicion of chronic pulmonary disease or any further confounding illness.^[18] Compared to placebo, all active treatments (myrtol, cefuroxime, and ambroxol) were well tolerated and safe, but evidently superior in terms of efficacy,

resulting in a more rapid and complete recovery. Myrtol® standardized tended to be superior to cefuroxime and ambroxol for several ancillary criteria, offering a well-evidenced alternative to antibiotics for acute bronchitis without specific microbial agent.

The superiority of Myrtol® (GeloMyrtol® forte) in treating acute bronchitis, comparing with placebo, was also shown in the multicenter, randomized, double-blind, placebo-controlled clinical trial, published by Gillissen *et al.* in 2013.^[19] Patients with acute bronchitis, without significant comorbidities or relevant comedication, were enrolled and divided into two groups, those receiving placebo and those treated with GeloMyrtol® forte 300 mg four times daily. The compliance and tolerability of the treatment were almost 100% for both categories. The efficacy of the examined medication was significantly superior toward placebo regarding the reduction of coughing fits (the median time to 50% reduction in coughing attacks per day was statistically significantly shorter, there were more patients without daytime coughing attacks, less difficulty to expectoration and less sleep disturbance due to nighttime coughing). Under treatment with Myrtol® less symptomatic impairment (composite bronchitis severity score and subscores) was observed, and significant more patients had a clinically satisfying response to the investigational medication.

Both studies shown that Myrtol® can be a well tolerable and safe alternative medication toward antibiotic therapy in patients with acute bronchitis without evidence of bacterial infection and without other underlying respiratory diseases, leading to rapid relief of major symptoms such as coughing attacks and difficulty to expectoration.

Chronic bronchitis

Myrtol® standardized is also investigated as a long-term treatment in patients with chronic bronchitis during winter time. In this context, a multicenter, placebo-controlled, double-blind, randomized parallel-group trial was conducted from Meister *et al.* to investigate the efficacy and tolerability of Myrtol® standardized (GeloMyrtol® forte) in doses of 3 × 300 mg daily.^[20] The investigational treatment (GeloMyrtol® forte or placebo) was taken for at least 1 month, and study subjects were evaluated in terms of efficacy (exacerbation rate, need for antibiotics, symptom scores, and general well-being) for a protocol-defined period of 6 months.

According to the study results, patients with acute exacerbation of chronic bronchitis were less ($P < 0.01$) in the myrtol standardized group compared to placebo group. In the placebo group, there was an evident peak of exacerbations incidence during the 3rd month of treatment, which was not observed in the active treatment group. In the GeloMyrtol® forte group, few patients with an acute exacerbation required antibiotics and few patients required them for more than 7 days, whereas 76.7% of patients in the placebo group treated with antibiotics for exacerbation, needed antibiotics for more than 7 days. The secondary clinical markers of efficacy, such as well-being (in terms of general health and health impairment by cough and expectoration) and overall therapeutic efficacy evaluation score, were also significantly superior under treatment with GeloMyrtol® forte.

Therefore, long-term treatment with Myrtol® standardized in patients with chronic bronchitis is equally well tolerated as placebo, but is clearly superior in efficacy, in terms of protecting against acute exacerbations, reducing the frequency and intensity of acute exacerbations, the need of antibiotics during an exacerbation, and the health impairment by cough and expectoration.

Chronic obstructive pulmonary disease

While Myrtol standardized is established in the treatment of acute and chronic bronchitis and sinusitis, research has been also done in

patients with COPD. Rantzsch *et al.* investigated the ability of essential oils to reduce cytokines release and production of ROS derived from *ex vivo* cultured alveolar macrophages taken from patients with COPD, GOLD Stadium III–IV.^[21] The alveolar macrophages were precultured with essential oils (Myrtol, eucalyptus oil, and orange oil) for 1 h and then stimulated with lipopolysaccharide (LPS) (1 µg/ml). Cellular ROS and tumor necrosis factor (TNF)-alpha, interleukin (IL)-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) secretion were measured after 4 h and 20 h, respectively. In comparison with negative controls, all essential oils tested had effective antioxidative properties, reducing significantly the ROS release in *ex vivo* cultured and LPS-stimulated alveolar macrophages. Only Myrtol inhibited significantly the release of TNF-alpha and GM-CSF, indicating additionally an anti-inflammatory activity in comparison with eucalyptus oil and orange oil. The reduction of TNF-alpha was only an early effect, which could not be further stimulated, and the reduction of IL-8 was inconsiderably.

However, except of its anti-inflammatory and antioxidative effects in COPD, Myrtol® standardized (in form of GeloMyrtol® forte) was also investigated for its antimicrobial effect in an animal model.^[22] Ninety-three experimental rats were exposed to cigarette smoke for a period of 12 weeks, and they developed pathological lung alterations similar to those of COPD patients. The investigation subjects were then randomly divided into six groups, according to their treatment with Myrtol® standardized or not and their intratracheal inoculation with *Pseudomonas aeruginosa* (PA) or not. All animals after smoke exposure had a significantly greater number of MUC5AC-positive cells in the bronchial epithelial cells and significantly increased expression levels of TNF-alpha and IL-6 after PA infection. However, the administration of Myrtol® standardized significantly attenuated the MUC5AC hypersecretion and reduced the production of IL-6 and TNF-alpha in the PA infected lungs, indicating a secretolytic and anti-inflammatory effects. Similarly, the bacterial load of PA-infected lungs was significantly lower in the subjects receiving GeloMyrtol® forte compared to those who did not receive the drug, providing evidence of the directly mediated antibacterial activity of the medication.

The clinically relevant effect of GeloMyrtol® forte in terms of effectiveness and tolerance was tested in patients with chronic obstructive bronchitis in a double-blind study involving GeloMyrtol® forte against placebo. Ulmer and Schött^[23] found that clinical parameters such as sputum volume and sputum color, ability to expectorate, attacks of coughing, general coughing, and shortness of breath were distinctly better in patients under 14-day treatment with GeloMyrtol® forte in comparison to placebo. On conclusion, both patients and physicians assessed positively the effectiveness of GeloMyrtol® forte, and both subjective and objective tolerance was excellent.

Myrtol® standardized is also clinically tested in acute exacerbations of COPD (AECOPD). Ninety-eight patients with AECOPD were randomly divided into a group treated with 300 mg three times daily Myrtol® standardized and a control group while all patients received the conventional treatment. The treatment group was also given “Qi-invigorating” which is a Chinese tonic herbs. After 2 weeks of treatment, a significant improvement of clinical symptoms, blood gas analysis parameters ($\text{PaO}_2/\text{FiO}_2$ and PaCO_2), and pulmonary function parameters (forced expiratory volume [FEV] 1 and FEV1%) was observed in patients treated with Myrtol® standardized in comparison to the control group.^[24]

Pediatric population

The medication is also tested in a pediatric population. A multicenter surveillance study examined the tolerability, safety, and efficacy in terms of clinical signs and symptoms of Myrtol® standardized (GeloMyrtol®

and GeloMyrtol® forte) in 511 children (4–12 years of age) with acute and chronic sinusitis, bronchitis, and sinus-bronchitis.^[25] More than 90% of the participants shown a complete recovery from trigeminal pain, headache, paranasal sensitivity, and mucus in the pharynx after 2 weeks of treatment. The adverse drug events were observed in a very low incidence of 1%, and the subjective efficacy was evaluated as very good or good by the majority of physicians, patients, and parents. Most of the children (>80%) experienced no difficulty in swallowing the capsules.

CONCLUSION

Myrtol® standardized, as the active substance of GeloMyrtol® and GeloMyrtol® forte, has a well clinically and experimentally demonstrated antioxidative, anti-inflammatory, and antibacterial potential while many studies confirmed its secretolytic effect. As such, the medication is proposed to be initiated in several acute and chronic infections of the upper and lower airway system as acute and chronic rhinosinusitis, acute and chronic bronchitis, and COPD. The potential advantages toward antibiotic therapy, such as the development of resistance and side effects, give clinicians a therapeutic alternative, especially in cases when diagnosis of bacterial infection is getting dubious.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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