Erciyes Med J 2021; 43(1): 3–8 • DOI: 10.14744/etd.2020.34467
INVITED REVIEW – OPEN ACCESS

Efficacy and Safety of Myrtol® Standardized in the Treatment of Acute and Chronic Rhinosinusitis: A Review of Literature

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Cite this article as:
Perić A, Soklič Košak T, Aleksić A, Kopacheva-Barsova G, Perić AV. Efficacy and Safety of Myrtol® Standardized in the Treatment of Acute and Chronic Rhinosinusitis: A Review of Literature. Erciyes Med J 2021; 43(1): 3-8.

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Submitted
17.06.2020

Accepted
26.08.2020

Available Online Date
12.12.2020

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ABSTRACT

The clinical pattern of rhinosinusitis is based on key symptoms, such as nasal obstruction/congestion, nasal secretion with postnasal discharge, facial pain with pressure, and impaired sense of smell. Acute rhinosinusitis is a viral infection commonly caused by impaired paranasal sinus aeration and drainage and can progress to bacterial superinfection. Chronic rhinosinusitis is an inflammatory disease of the sinonasal mucosa with symptoms persisting for more than 12 weeks. This paper aimed to summarize and update the literature related to the use of herbal product Myrtol® standardized in the treatment of acute and chronic rhinosinusitis. Earlier investigations have demonstrated that Myrtol® standardized has strong secretolytic, secretomotoric, anti-inflammatory, antioxidative, and antimicrobial effects. Therefore, this study reviewed randomized studies related to its use in the treatment of upper-airway inflammations and discussed the mechanisms of action of this herbal drug on infected nasal and paranasal sinuses mucosa.

Keywords: Sinusitis, rhinitis, herbal medicine, plants, medicinal

INTRODUCTION

Acute rhinosinusitis (ARS) is a sudden-onset inflammation affecting the mucosa of the nasal cavity and paranasal sinuses for no more than 12 weeks (1, 2). Approximately 98%–99.5% of the cases of ARS are caused by viruses, particularly rhinoviruses, coronaviruses, influenza and parainfluenza viruses, and adenoviruses (1–3). This viral upper-airway infection, also known as common cold, usually occurs for 10 days with or without symptomatic therapy. However, in some cases, it can be followed by postviral ARS, with a prolonged duration of nasal complaints requiring medications, or secondary bacterial infection (only 0.5%–2% of ARS cases) (2–4). Chronic rhinosinusitis (CRS) is diagnosed based on symptoms persisting for more than 12 weeks and the presence of mucosal edema with or without nasal polyps as revealed by nasal endoscopy and computed tomography (CT) scan of the paranasal sinuses (1, 2, 5). However, its etiology remains unknown, and the mechanisms involved in the translation from ARS to CRS are still under debate, including recurring viral, bacterial, and fungal infections; allergic reactions; neurogenic inflammation; and innate and adaptive immune dysfunction, as well as other factors such as cigarette smoking and air pollution (1, 2, 5).

Local symptoms of ARS and CRS (nasal obstruction, rhinorrhea, postnasal discharge, facial pain/pressure, impaired sense of smell) are caused by infection-stimulated production of inflammatory mediators in the respiratory epithelium. The changes in the function of ciliated respiratory epithelial cells lead to impaired mucociliary clearance (1–3, 5–7). The sense of smell may be affected by mucosal edema that cause the physical restriction of airflow and odorants to the olfactory area or may be due to an inflammation that affects the mucosa of the olfactory cleft (6, 7).

ARS is commonly treated with antibiotics, intranasal or oral corticosteroids, nasal irrigation solutions, decongestants, mucolytics, antihistamines, and herbal medicinal products (1–3). However, as ARS most frequently a viral disease, antibiotics are administered only in cases of strong bacterial infection. On the other hand, regardless of the presence of nasal polyps, CRS is primarily treated with intranasal corticosteroids, or other medications such as macrolide antibiotics, nasal irrigation solutions, systemic glucocorticoids, antihistamines, and biological drugs (1–3).

Herbal medicines have been used for centuries for the treatment of many disorders. In 2011, the World Health Organization estimated that 70%–90% of populations in developing countries and almost 20% in the United States used herbal drugs, whereas in Europe, only 10%–20% (8, 9). Myrtol® standardized, also known as GeloMyrtol® and GeloMyrtol® forte, with codifying number ELOM-080, is an herbal medicine formulated through distillation of essential oils. The main active ingredients of this drug are monoterpenes: d-limonene, 1,8-cineole, and α-pinene,

extracted from lime (Citrus aurantifolia), eucalyptus (Eucalyptus globulus), and pine (Pinus spp.), respectively. The pharmacodynamic profile of Myrtol® standardized is classically characterized by mucosecretolytic properties, with supplementary effects such as antioxidant, anti-inflammatory, antibacterial, and bronchospasmolytic effects based on extensive clinical research (10–12). The antioxidative effects are of particular clinical importance in chronic inflammatory disorders (11, 12), resulting in its widespread use in the treatment of acute and chronic upper and lower respiratory tract infections, such as ARS and CRS, acute and chronic bronchitis, and chronic obstructive pulmonary disease. However, according to the European Position Paper on Rhinosinusitis and Nasal Polyps in 2012 and 2020, two leading European guidelines for diagnosis and treatment of rhinosinusitis, Myrtol® standardized is recommended only for postviral ARS (1, 2). This drug is available as enteric-coated capsules in two dosage forms containing 300 mg (GeloMyrtol® forte) or 120 mg (GeloMyrtol®) active substances. For adult patients and children aged 6 years and above, it is recommended to prescribe GeloMyrtol® forte 1 capsule 3–4 times daily or GeloMyrtol® 2 capsules 3–4 times daily to treat acute airway inflammation, and GeloMyrtol® forte 1 capsule twice daily or GeloMyrtol® 2 capsules twice daily for chronic inflammation.

Clinical and Research Consequences

Pharmacological effects of Myrtol® standardized

A pharmacokinetic study showed that the rapid absorption of the medication by enteric epithelium and rapid reach of high-level concentration of medication in plasma are prevented by enteric coating of the capsules, resulting in a plateaued concentration in plasma only a few hours after the medication use (13). The main components of Myrtol® standardized are absorbed into the body, and as they enter the bloodstream, this medication reaches the nasal and paranasal sinus mucosa and the smallest branches of the bronchial tubes (13).

The effect of Myrtol® standardized on mucociliary clearance is the drug's most important pharmacological mechanism. In an experimental study by Begrow et al. (14), ciliary beat frequency (CBF) was measured in rat tracheal explants by high-speed video camera linked to a digital microscope. The characteristics of mucociliary clearance were determined by microdialysis technique, measuring the acceleration of mucus clearance in a tracheal wall. Results showed that Myrtol® standardized accelerated both mucociliary transport and CBF dependent on the concentration (14). Through a saccharine test, Han et al. (15) demonstrated that treatment with Myrtol® standardized for 10 days increased the nasal mucociliary transport velocity and nasal patency in patients with chronic rhinitis. A recent investigation on cultured human nasal epithelial cells showed that Myrtol® standardized increased the mucus production from goblet cells in the short-term and promoted ciliated cell differentiation in the long-term use (16).

Myrtol® standardized also has strong anti-inflammatory and antimicrobial effects. Grassmann et al. (17) showed that its active compounds, especially 1,8-cineole, can inhibit the leucocyte activation during the inflammatory process, resulting in a decrease in the amount of OH-type reactive oxygen radicals. These free radicals can cause strong damage of upper and lower respiratory tract epithelium, especially in patients with chronic inflammatory disorders. During the inflammatory process, Myrtol® standardized captures that hydroxyl radicals, the most aggressive OH-type oxygen radicals, and choke the leucocyte activation. These reactions are presumably lipophilic interactions with the leucocyte membranes in which the signal transfer is extensively changed so that hyperactivation is prevented and oxidative cell damage is thus avoided (17). The same active compound of Myrtol® standardized inhibits the activity of 5-lipooxygenase, produced by human basophils and eosinophils, resulting in lower production of leukotriene C4/D4/E4 in the nasal mucosa and bronchial tubes (18). Disturbance of the mucociliary transport in the nasal mucosa results in mucostasis and increases the nasal secretion viscosity, thereby increasing the risk of bacterial infection. The etiologically most important bacteria in ARS are Streptococcus pneumoniae and Haemophilus influenzae (1–3). Myrtol® standardized has been tested in the different concentrations on the above microbial spectrum of patients with acute bronchitis and showed a dose-dependent inhibition in the growth of both organisms (19).

Side effects of Myrtol® standardized

Myrtol® standardized is a well-tolerated and safe medication in both adult and pediatric patients. In very rare cases, hypersensitivity reactions (e.g., rash, pruritus, facial swelling, shortness of breath, or circulatory disturbances) may occur. By literature review, we found only one case of an anaphylactic shock that developed after administering Myrtol® standardized to treat ARS (20). In this case, itching, urticaria, and respiratory distress syndrome developed approximately 20 minutes after the use of this medication. Skin prick test was highly positive for the dibutyl phthalate, a component from the capsule coating (20). In rare cases, patients reported gastrointestinal disturbances, e.g., stomach pain, or complaints in the upper abdomen. Nausea, vomiting, diarrhea, or other digestive problems rarely occur, especially in patients on long-term therapy of CRS by Myrtol® standardized. Very rarely, patients may experience impairments in the sense of taste or headache or existing kidney stones and gallstones may start to move (20).

Randomized studies on the use of Myrtol® standardized in the treatment of ARS and CRS

A review was performed on available literature including randomized, prospective studies published in the PubMed and Google Scholar databases. The search terms were as follows: "Myrtol® standardized," "GeloMyrtol®," "GeloMyrtol® forte," and "acute rhinosinusitis" and "Myrtol® standardized," "GeloMyrtol®," "GeloMyrtol® forte," and "chronic rhinosinusitis." There were only five randomized studies on the effects of Myrtol® standardized in patients with ARS (three with adult patients, and two with pediatric population) and two randomized studies on the effects of same medication on adult patients with CRS without nasal polyps. Studies in which the study groups were not homogenous were excluded. One study performed in China involving 160 adult patients was excluded due to enrolment of patients with ARS and CRS (21). Therefore, a large-scale study with 511 children (aged 4–12 years) was also excluded, because it involved patients with ARS and CRS accompanied by acute and chronic bronchitis (22). Finally, three studies on ARS (Table 1) and two studies on CRS (Table 2) were included for analysis.

Federspil et al. (23) conducted a randomized, multicenter, double-blinded, placebo-controlled study including 330 patients with

Table 1. Randomized studies including the patients with acute rhinosinusitis treated by Myrtol® standardized

Study	Methods	Participants	Therapy	Outcomes	Results
Federspil et al. (1997) (23)	Randomized, double-blinded, placebo-controlled study	Acute postviral rhinosinusitis (n=330)	• Myrtol® standardized, 4 capsules of 300 mg daily for 6±2 days (n=109) • Essential oil (unregistered), four capsules of 300 mg daily for 6±2 days (n=110) • Placebo, four capsules daily for 6±2 days (n=111) All patients received xylometazoline nasal spray, two puffs in each nostril daily for four days	Difference in symptom score before and after treatment at day 14	• Myrtol® standardized and the other essential oil proved to be significantly superior to placebo • Tolerance was slightly better for Myrtol® standardized in comparison to the essential oil
Karpova et al. (2016) (24)	Randomized, parallel-group, comparative study	Uncomplicated acute rhinosinusitis (n=60)	• Myrtol® standardized, three capsules of 120 mg daily for seven days + antibiotic + decongestant + nasal irrigation solution for seven days (n=30) • Antibiotic + decongestant + nasal irrigation solution for 7 days (n=30)	Differences in VAS improvement for rhinorrhea, nasal congestion, and cough in Myrtol® standardized group at days 7 and 14	• Myrtol® standardized proved to be superior to standard therapy of uncomplicated acute rhinosinusitis in children • Tolerance was similar in both treatment groups
Gottschlich et al. (2018) (25)	Prospective, parallel-group, comparative study	Uncomplicated acute rhinosinusitis (n=223)	• Myrtol® standardized, four capsules of 300 mg daily for 14 days (n=114) • BNO 1016, three tablets of 160 mg daily for 14 days (n=109)	Difference in facial pain score before and after therapy at day 14	• Myrtol® standardized proved to be significantly superior to BNO 1016 regarding the improvement of facial pain • Tolerance was similar in both treatment groups

postviral ARS. These patients were randomly divided into three groups to receive (i) Myrtol® standardized (n=109) (4 capsules of 300 mg daily), (ii) another essential oil prepared for this investigation (n=110) (4 capsules of 300 mg daily), and (iii) placebo (n=111) (4 capsules daily) for 6±2 days. The primary outcome was the total symptom score of seven nasal symptoms (nasal obstruction, nasal secretion, pain upon pressure, fever, pain at bending over, headache, general health status). Their results demonstrated no significant difference in the post-treatment total symptom score at day 14 after the treatment was initiated between participants with ARS treated by Myrtol® standardized and essential oil, but both herbal preparation groups were superior to placebo group. Safety was slightly better with Myrtol® standardized in comparison to the essential oil (23). In this study, Myrtol® standardized was investigated as an alternative to treat postviral ARS, where the bacterial infection is uncertain. According to the last two European Position Papers on Rhinosinusitis and Nasal Polyps, in 2012 and 2020, postviral ARS is defined as an inflammation of the sinonasal mucosa that have symptoms (nasal obstruction/congestion, anterior nasal secretion, postnasal discharge, facial pain with the sense of pressure, and/or impaired sense of smell) obvious after 5 days or persistent after 10 days within less than 12 weeks (1, 2). Federspil et al. (23) showed the significance in the improvement of ventilation and drainage of paranasal sinuses using an herbal secretolytic, secretomotoric, and anti-inflammatory drug in patients with postviral ARS as a good alternative to antibiotics, synthetic mucolytics, and intranasal corticosteroids. Antibiotics should be strictly selected for patients with confirmed bacterial ARS due to increased resistance to antibiotics.

Karpova et al. (24) organized a comparative, non-placebo-controlled study that included 60 children aged from 6 to 10 years on out-patient and clinical treatment of uncomplicated ARS. The patients in the Myrtol® standardized group (n=30) were treated with Myrtol® standardized 120 mg 3 times/day in conjunction with the standard therapy for ARS comprising oral antibiotics, decongestants, and a nasal irrigation solution for 7 days. Those in the "standard rhinosinusitis therapy" group (n=30) received only standard therapy for ARS also for 7 days. Karpova et al. used a Visual Analogue Scale (VAS) score to evaluate the intensity of the three symptoms of rhinosinusitis: rhinorrhea, nasal congestion,

Table 2. Randomized studies including the patients with chronic rhinosinusitis treated by Myrtol® standardized

Study	Methods	Participants	Therapy	Outcomes	Results
De Mey and Riechelmann (27)	Multicenter, randomized, double-blinded, placebo-controlled	Chronic rhinosinusitis without nasal polyps (n=48)	• Myrtol® standardized, 3 capsules of 300 mg daily for 3 months (n=24) • Placebo, 3 capsules daily for 3 months (n=24)	Difference in Lund-Mackay CT score	• Myrtol® standardized is significantly superior to placebo in terms of the decrease of Lund-Mackay CT score • Tolerance was slightly better for placebo than for Myrtol® standardized (3 patients from Myrtol group reported nausea)
Wu and Tang (28)	Prospective, randomized, comparative study	Chronic rhinosinusitis without nasal polyps (n=69)	• Myrtol® standardized, 3 capsules of 300 mg daily + ephedrine 1% nasal drops, for 3 months (n=41) • Chlorpheniramine oral tablets, four tablets of 4 mg + ephedrine 1% nasal drops, for 3 months (n=28)	Significantly higher total effective rates in patients treated by Myrtol® standardized	• GeloMyrtol® forte is more effective in therapy of CRS in comparison to chlorpheniramine

and cough. The results showed significant reduction in VAS for all three symptoms in days 7 and 14 in the Myrtol® standardized group than in standard rhinosinusitis therapy group. No adverse reaction was observed in the Myrtol® standardized group that could be attributable to the mechanism of the drug (24). This study demonstrated that Myrtol® standardized is safe and clinically effective for the treatment of the uncomplicated forms of ARS in children, indicating its potential for wide practical application as a good additional/alternative to antibiotics.

In a prospective, non-interventional, parallel-group, non-placebo-controlled trial by Gottschlich et al. (25), a total of 223 patients with uncomplicated ARS were treated for a maximum of 14 days with either five-compound herbal drug BNO 1016 (Sinupret® forte) (3 tablets of 160 mg daily, n=109) or Myrtol® standardized (4 capsules of 300 mg daily, n=114). Their results revealed that recovery of facial pain was faster with Myrtol® standardized, starting from day 3, than with BNO 1016. The evaluation of facial pain intensity at the end of the first week of therapy indicated that the reduction of pain in patients receiving Myrtol® standardized was 1.2 days ahead compared to patients treated by BNO 1016. At day 14, Gottschlich et al. found that the facial pain score was significant improved in patients treated by Myrtol® standardized than in those on therapy by BNO 1016 (p=0.0147). Therefore, Myrtol® standardized also result in significantly higher patient satisfaction regarding the improvement of feeling of general illness. However, the patients reported that both drugs were equally well tolerated (25). This was the only investigation comparing the efficacy and safety of Myrtol® standardized and BNO 1016, and comparative studies with herbal medicines are very rare. On the other hand, Tesche et al. (26) performed a double-blinded, randomized study to compare BNO 1016 and 1,8-cineole, a strong monoterpene and a key pharmacological constituent of Myrtol® standardized, in 150 patients with non-purulent ARS (BNO 1016 group, n=75; 1,8-cineole, n=75). The primary endpoint was the sum of all nasal symptoms (frontal headache, headache on bending, nasal obstruction, nasal secretion, the amount of nasal secretion, viscosity of nasal secretion, fever, sensitivity of pressure points of trigeminal nerve, and general condition) within 7 days. Results showed clinically relevant and significant better improvement in the 1,8-cineole group than in the BNO 1016 treatment group after 4 and 7 days ($p<0.0001$) (26). The 1,8-cineole is a well-known herbal compound with strong anti-inflammatory, secretolytic, antimicrobial, and secretomotoric effects accelerating the beat frequency of respiratory epithelium cilia, resulting in direct action on the pathophysiological mechanisms of rhinosinusitis (26).

De Mey and Riechelmann (27) organized a randomized, multicenter, double-blind, placebo-controlled study investigating the effects of GeloMyrtol® forte versus placebo in patients with CRS. This study enrolled 48 patients with CRS, diagnosed by symptoms and endoscopic and radiological (CT) findings on the paranasal sinuses, assessed as the Lund-Mackay CT score. The patients with anatomical variations in the region of the nasal cavity and paranasal sinuses, with nasal polyps and asthma, who underwent surgeries in the sinonasal region, and who were administered corticosteroid therapy were excluded from this investigation. The main objective criterion of selection and clinical evaluation of patients with CRS was the Lund-Mackay CT score because symptoms of CRS can

be missed or vary in intensity. The patients received GeloMyrtol® forte (3 capsules of 300 mg daily) or placebo (thrice daily) for 12 weeks. At the end of the treatment, the GeloMyrtol® forte group showed significantly lower Lund-Mackay score than the placebo group whose radiological findings were unchanged (27).

In a randomized study performed in China by Wu and Tang (28), 69 patients who were diagnosed with CRS were all treated with 1% ephedrine nasal drops. Group 1 (n=41) received GeloMyrtol® forte (3 capsules of 300 mg daily), while Group 2 (n=28) was treated with antihistamine chlorpheniramine (3 tables of 4 mg daily) for 12 weeks. The remission time for GeloMyrtol® forte group was 5.3±3.7 days and for chlorpheniramine group was 6.9±3.4 days, without significance difference between two groups. However, the total effective rates were 78.1% in GeloMyrtol® forte group and 39.3% in chlorpheniramine group ($p<0.01$). Wu and Tang (28) concluded that GeloMyrtol® forte is a more effective medication in treating CRS than antihistamine.

CONCLUSION

To the best of our knowledge, this is the first review that focused exclusively on the treatment of ARS and CRS by Myrtol® standardized. Although this herbal drug is administered in the treatment of upper respiratory tract infections, we interestingly found only five randomized studies investigating the efficacy and safety of this medicine: three on the treatment of ARS and two on CRS without nasal polyps. However, only two studies were designed and conducted as placebo-controlled studies: one for ARS and one for CRS. This small number of available literature is the main limitation of this review. With its well-established strong secretolytic, secretomotoric, antioxidative, anti-inflammatory, and antimicrobial effect, Myrtol® standardized can be a good addition in antibiotic treatment and a good alternative to antibiotics in patients with uncomplicated ARS, especially with "postviral" ARS. Myrtol® standardized is generally a well-tolerated and safe medication in both adult and pediatric patients. Gastrointestinal side effects may rarely occur, especially in patients on long-term therapy of CRS.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – AP; Design – AP, TSK; Supervision – AP; Data Collection and/or Processing – AP, AVP; Analysis and/or Interpretation – AP, TSK, AA, GKB; Literature Search – AP, TSK, AA, GKB, AVP; Writing – AP; Critical Reviews – AP, TSK, AA, GKB, AVP.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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