

# Effect Of Each Pelargonium Sidoides And Echinacea With Azithromycin On Recurrent Tonsillitis In Pediatrics

Original  
Article

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## ABSTRACT

**Purpose:** Repeated attacks of tonsillitis is a common disease affecting children. The aim of this study was to investigate the possible protective influence of adjunct use of each Echinacea and pelargonium sidoides separately with oral Azithromycin (AZT), compared to use of AZT alone in children with recurrent attacks of acute tonsillitis.

**Methods:** A prospective randomized controlled trial including four groups of children with recurrent tonsillitis. Group A: "control group" not received any prophylactic medications. Group B: Received a prophylactic dose of AZT (10 mg/kg/day, not exceeds 500mg/day). Group C: Received AZT as in group B plus 250 mg of Echinacea extract 3 times daily. Group D: Received AZT as in group B plus 10-20 drops of pelargonium sidoides extract according to age, 3 times daily. In all children who receive medications, the duration of treatment is fixed as to cover 10 consecutive days per month for 6 months. The number and severity of tonsillitis were assessed and compared in different groups.

**Results:** Group B, group C and group D had significant less number of tonsillitis attacks and severity of assessed symptoms during 6 months of prophylactic treatment in comparison to control group A, with significant results in group C (i.e. AZT plus Echinacea) and group D (i.e. AZT plus pelargonium sidoides) compared to group B (i.e. AZT alone)

**Conclusion:** The combination of Echinacea or Pelargonium sidoides with AZT achieved better results in prevention of recurrent tonsillitis attacks than AZT alone in pediatric patients with recurrent attacks of tonsillitis.

**Key Words:** Azithromycin; echinacea; pelargonium; sidoides; tonsillitis

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## INTRODUCTION

Acute tonsillitis is one of the most frequently recorded disease by ENT, pediatricians and primary care physicians all over the world<sup>[1,2]</sup>

Epidemiological studies show that tonsillitis are seen more in age group 3–12 years-old with 69% frequency because of the relatively immature immune system with more vulnerability to viral infections and other socio-environmental factors<sup>[3]</sup>

Acute tonsillitis is defined as acute appearance of typical clinical symptoms, including sore throat with or without difficulty swallowing, tonsillar enlargement with potential presence of pus, congestion, enlargement of cervical lymph nodes, fever and fatigue. Other symptoms may be present like palatal petechiae, strawberry tongue, red swollen uvula, or skin rash. Such patients account for about 5% visits to a doctor, and 50% of them are aged 5 to 15 years, which interfere with daily activities, resulting in absence from school and/or work for their parents<sup>[4,5,6]</sup>

The universal outbreak of the new coronavirus COVID-19 and its pandemic global spread according to WHO declaration in early 2020 has compelled an international

change in health service. Postponing elective surgeries as tonsillectomy is one of these changes with shifting more to the medical side rather than surgery<sup>[7]</sup>

Tonsillectomy is usually indicated when a patient had 6 or more acute tonsillitis attacks during last year and not recommended with less than 3 attacks. The choice of medical treatment will rise in case of less number of attacks or any condition not fulfilling the surgical requisites<sup>[8,9]</sup>.

Antibiotics are prescribed for managing acute and recurrent attacks of tonsillitis. However, antibiotics reduce the risk of recurrent tonsillitis complications as rheumatic fever and acute glomerulonephritis, limiting its excessive prescription is a major goal because of development of antibiotic resistant strains of bacteria. From this point of view, the application of alternative medicine rises and get popularity<sup>[10]</sup>

Azithromycin (AZT) is one of antibiotics which used in treatment of acute tonsillitis and considered better than injectable benzathine penicillin regarding patient compliance and hypersensitivity hazards. Also it is distributed throughout the body with a high concentration in tonsils with minimally noticed adverse effects<sup>[11]</sup>

Gopal *et al*<sup>[12]</sup> reported that use of 500 mg once weekly oral AZT was effective in prevention of streptococcal pharyngeal infection compared to oral penicillin therapy. Also, AZT has no ability to induce cytochrome P450 IIIA enzyme system so it has minimal adverse effects and minimal drugs interactions<sup>[11]</sup>

Herbal medicines have been used for centuries to treat acute upper airway infections. According to Ogal *et al* <sup>[13]</sup> the findings strongly support the use of Echinacea for the long-term prevention of RTIS, cold days, influenza and other enveloped virus infections, RTI complications, and antibiotic use in children aged 4 to 12.

Echinacea was found to produce profound effects on immune cells such as an increase in respiratory cellular activity, lymphocyte activation, macrophages, phagocytosis, natural killer cell cytotoxicity and granulocyte migration<sup>[14,15]</sup>

The roots of pelargonium sidoides has been used for decades in Africa for treatment of infections especially respiratory tract infection because of its antibacterial and antiviral properties<sup>[16]</sup>

Pelargonium sidoides (EPs 7630) has significant anti-adhesive and anti-invasive capabilities<sup>[17,18]</sup>Also, pelargonium sidoides has an immune-modulatory property that mediated through the release of tumor necrosis factor (TNF- $\alpha$ ) and nitric oxide, as well as the stimulation of interferon-gamma and an increase in natural killer cell activity<sup>[19]</sup>

The aim of this study was to detect the beneficial effect of combined use of each Echinacea and pelargonium sidoides separately with oral AZT, compared to use of AZT alone in prophylaxis of acute tonsillitis in children concerning the frequency of tonsillitis attacks and intensity of symptoms.

## MATERIAL AND METHODS

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### Study design

Prospective randomized controlled clinical trial.

The study was conducted during the period from January 2021 to December 2022 and was approved by the Committee for Medical Research Ethics. All patients' parents provided a written formal consent prior to enrollment in the study. No pharmaceutical companies funded this study or contributed to the study setting, result evaluation or writing of this study. So, this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that they have no conflict of interest.

### Patients

400 pediatric patients were included in this study. They were collected either from the ENT outpatient clinic or from the general pediatric outpatient clinic during a period of 18 months. It was done at nearly rate of 5 to 6 included patients per one week, which in turn was easily collected from 2 separate clinics. All patients had the criteria of recurrent tonsillitis that not indicated for tonsillectomy or if the surgical option was refused by the parents. Both sexes were included with an age range from 3 to 13 years. Clinical picture of acute tonsillitis was fever, sore throat at rest and at swallowing, hyperemia and swelling of tonsils with or without purulent discharge on tonsils, and cervical lymphadenitis.

### Exclusion criteria

- Complications of chronic tonsillitis as rheumatic heart disease or glomerulonephritis.
- Patients not feasible to medical treatment as in OSAS.
- Conditions affecting the immune status as diseases like autoimmune diseases, DM and neoplasms, or as drugs like steroids, immune suppressive drugs and chemotherapy.
- Patients on long acting penicillin.
- Hypersensitivity to any drug used.

### Grouping

The patients were randomly included into one of the four groups using the software (StatSoft - random number generator)for randomization that was performed for each patient signing the informed consent. Patients were randomized equally in four groups.

**Group A:** Control Group who didn't receive any prophylactic medications.

**Group B:** Received a prophylactic dose of AZT (10 mg /kg/day, not exceeds 500mg/day) either in the form of oral suspension (100 mg or 200 mg /5ml) or tablet form (250 mg tablet). The calculated dose was taken once per day (1 hour before or 2 hours after meal) for 6 consecutive days per month for 6 months.

**Group C:** Received both AZT as in group B and commercially available Echinacea extract in a dose of 250 mg of Echinacea (Immulant, Mebaco – Arab Co), 3 times daily for 10 consecutive days per month for 6months.

**Group D:** Received both AZT as in group B plus commercially available Pelargonium sidoides extract (Kalobin, Marcyrl Pharmaceutical Industries) in a dose of

10 drops of Pelargonium sidoides in patients below 6 years old and 20 drops in patients above 6 years old, 3 times daily for 10 consecutive days per month for 6 months.

### Intervention

All patients had completed general and local ENT examination after assessing a complete history regarding the rate of attacks of acute tonsillitis and regarding the severity of symptoms.

The pretreatment period was equally fixed in all groups to be the previous 6 months before enrollment in the study.

The prophylactic treatment was in a period of 6 months in all cases. In this time, the data was collected at monthly based visits with confirming the prophylactic regimen in the 3 study groups; B, C and D. Patients compliance was assessed and any drug drawback symptoms were recorded.

### Outcome measures

All the data were collected and analyzed in every visit during the study period (6 months). The first baseline data represent the condition before prophylactic treatment that was compared to the subsequent 6 months after treatment.

In each visit, the number of acute tonsillitis attacks were recorded in all groups, and any complain of arthralgia, fever or sore throat were also recorded separately. The questions were carefully directed to both parents with the necessity of obtaining clear and frank answers in order to ensure accurate and unbiased results.

### Statistical Analysis

In order to analyze the data, descriptive statistics were used either for qualitative parameters (numbers and percentage) or quantitative parameters (number, mean, standard deviation, minimum and maximum values).

The probability of  $<0.05$  was used as a cut-off point for all significant tests.

The analysis was performed using an IBM SPSS version 23.

## RESULTS

Four hundred patients were participated in this study, males 192 (48%) and females 208 (52%), aged from 3 to 13 years (mean age 3.5 years), and randomized either to a control group (A) or to the drug groups (B, C or D) to be finally one hundred in each group. Group A had no prophylactic treatment during the study period. Group B received oral AZT for 6 months of the study, Group C received oral Echinacea extract and oral AZT for 6 months of the study and Group D received oral Pelargonium sidoides extract and oral AZT for 6 months of the study.

There were no statistical significant difference regarding age and sex among all groups ( $P > 0.05$ ) (Table I).

**Table I:** Patients age and sex in the 4 study groups

	Group A	Group B	Group C	Group D	<i>P value</i>
Age: mean $\pm$ SD	9.92 $\pm$ 2.4	9.16 $\pm$ 1.5	9.39 $\pm$ 1.4	9.44 $\pm$ 1.5	0.025
Male %	41%	47%	50%	54%	0.307

The number of attacks among the preceding 6 months before enrollment in the study as well as the leading symptoms like sore throat and arthralgia were all had no significant difference between all four groups (Table II)

The outcome in drug groups (B, C and D) that was assessed during the 6 months of prophylactic period where compared with the pre-prophylactic period in each group separately showed statistical significant difference ( $P < 0.05$ ) regarding the number of attacks as well as the symptoms like sore throat, fever and arthralgia (Table III).

All patients in drug groups (B, C and D) had statistically significant less number of attacks and less frequency of the studied symptoms (sore throat, fever and arthralgia) when compared to patients in the control group (A) during the prophylactic treatment period.

Patients in group (C) (Table IV) and group (D) (Table V) had statistically significant less number of attacks and less frequency of the studied symptoms ( $P < 0.05$ ) when compared to patients in the group (B) during the prophylactic treatment period.

**Table II:** Comparison between the 4 groups regarding the number of acute tonsillitis attacks and the frequency of manifestations in all groups in the 6 months before the prophylactic treatment.

Clinical variable	Group A	Group B	Group C	Group D	<i>p value</i>
Number of attacks of acute tonsillitis	6.35 $\pm$ 1.2	6.36 $\pm$ 1.2	6.47 $\pm$ 0.8	6.34 $\pm$ 0.7	0.802
Sore throat	8.19 $\pm$ 1.6	8.11 $\pm$ 1.4	8.36 $\pm$ 1.4	8.10 $\pm$ 1.1	0.546
Fever mean $\pm$ SD	9.43 $\pm$ 1.0	9.42 $\pm$ 0.9	9.75 $\pm$ 1.5	9.91 $\pm$ 1.2	0.009
Arthralgia mean $\pm$ SD	7.82 $\pm$ 0.9	7.93 $\pm$ 0.8	7.99 $\pm$ 0.7	8.06 $\pm$ 0.6	0.207

**Table III:** Comparison between the period before and during prophylactic treatment regarding number of acute tonsillitis attacks and the frequency of manifestations among groups B, C and D.

Variable	Group B			Group C			Group D		
	before	after	<i>P value</i>	before	after	<i>P value</i>	Before	After	<i>P value</i>
Number of attacks Mean $\pm$ SD	6.36 $\pm$ 1.2	3.57 $\pm$ 1.8	< 0.001	6.47 $\pm$ 0.8	2.57 $\pm$ 0.50	< 0.001	6.34 $\pm$ 0.7	2.47 $\pm$ 0.5	< 0.001
Sore throat: mean $\pm$ SD	8.11 $\pm$ 1.4	5.67 $\pm$ .4	< 0.001	8.36 $\pm$ 1.4	3.50 $\pm$ 0.50	< 0.001	8.10 $\pm$ 1.1	3.47 $\pm$ 0.5	< 0.001
Fever mean $\pm$ SD	9.42 $\pm$ 0.9	6.47 $\pm$ 5	< 0.001	9.75 $\pm$ 1.5	3.46 $\pm$ 0.50	< 0.001	9.91 $\pm$ 1.2	3.43 $\pm$ 0.5	< 0.001
Arthralgia mean $\pm$ SD	7.93 $\pm$ 0.8	4.55 $\pm$ 1.0	< 0.001	7.99 $\pm$ 0.7	3.50 $\pm$ 0.50	< 0.001	8.06 $\pm$ 0.6	3.42 $\pm$ 0.50	< 0.001

**Table IV:** Comparison between group B and group C regarding the number of acute tonsillitis attacks and the frequency of manifestations during the 6 months of the prophylactic treatment.

Variable	Group B	Group C	<i>P value</i>
Number of attacks mean $\pm$ SD	3.57 $\pm$ 1.5	2.57 $\pm$ 0.50	< 0.001
Sore throat mean $\pm$ SD	5.67 $\pm$ 1.4	3.50 $\pm$ 0.50	< 0.001
Fever mean $\pm$ SD	6.47 $\pm$ 0.5	3.46 $\pm$ 0.50	< 0.001
Arthralgia mean $\pm$ SD	4.55 $\pm$ 1.0	3.50 $\pm$ 0.50	< 0.001

**Table V:** Comparison between group B and group D regarding the number of acute tonsillitis attacks and the frequency of manifestations during the 6 months of the prophylactic treatment.

Variable	Group B	Group D	<i>P value</i>
Number of attacks mean $\pm$ SD	3.57 $\pm$ 1.5	2.47 $\pm$ 0.50	< 0.001
Sore throat mean $\pm$ SD	5.67 $\pm$ 1.4	3.47 $\pm$ 0.50	< 0.001
Fever mean $\pm$ SD	6.47 $\pm$ 0.5	3.43 $\pm$ 0.50	< 0.001
Arthralgia mean $\pm$ SD	4.55 $\pm$ 1.0	3.42 $\pm$ 0.50	< 0.001

There was no significant difference between group (D) and group (C) in number of attacks and frequency of the studied symptoms during the prophylactic treatment period ( $P < 0.05$ ) (Table VI).

**Table VI:** Comparison between group C and group D regarding the number of acute tonsillitis attacks and the frequency of manifestations during the 6 months of the prophylactic treatment.

Variable	Group C	Group D	<i>P value</i>
Number of attacks mean $\pm$ SD	2.57 $\pm$ 0.50	2.47 $\pm$ 0.50	0.159
Sore throat mean $\pm$ SD	3.50 $\pm$ 0.50	3.47 $\pm$ 0.5	0.673
Fever mean $\pm$ SD	3.46 $\pm$ 0.50	3.43 $\pm$ 0.50	0.671
Arthralgia mean $\pm$ SD	3.50 $\pm$ 0.50	3.42 $\pm$ 0.50	0.259

No significant side effects were observed that require drug discontinuation, except for mild reversible GIT upset.

## DISCUSSION

In pediatrics, the recurrent attacks of tonsillitis have serious effects on the child's general and mental health so tonsillectomy is a common surgery among children. It is considered effective and safe operation; however, its effect on immunity is not clear until now<sup>[20]</sup>

Also, the global epidemic of the new coronavirus COVID-19 and its spread according to WHO declaration in early 2020 has obliged an international change in health service. Limiting elective surgeries as tonsillectomy is one of these changes with more acceptance of non-surgical option of treatment<sup>[7]</sup>

In current study AZT was given as a prophylactic treatment for recurrent tonsillitis alone or with Echinacea extract or with pelargonium sidoides extract. Children who received AZT only showed a significant decrease in number of attacks and severity of recurrent tonsillitis when compared to non-prophylactic group.

These results were in accordance to Abdel-Naby Awad<sup>[8]</sup> who adopted this new regimen for prevention of recurrent tonsillitis in pediatrics (60 mg/kg) of AZT divided on 6 consecutive days monthly for 6 consecutive months in his trial to get superior results to other previously proposed regimens.

As a support to the results of current study was Snider *et al.*<sup>[21]</sup> who demonstrated AZT efficacy as a prophylaxis in decreasing streptococcal infections and PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections).

However, the significant effect of AZT in decreasing the number and severity of recurrent tonsillitis attacks, it failed in complete prevention of recurrent attacks. Therefore, Pelargonium sidoides and Echinacea were tried each in combination with AZT aiming for achieving better results. It was reported that patients with recurrent tonsillitis may have deficient humoral antibodies compared to their age and sex-matched controls<sup>[10]</sup> Accordingly; we used Echinacea and Pelargonium sidoides in combination to AZT aiming to improve patients' immunity.

In current study the combined prophylactic therapy of AZT plus Echinacea extract had a significant results in decreasing the number and severity of recurrent tonsillitis attacks in comparison to AZT-only receiving group. This results was in accordance to Abdel-Naby Awad<sup>[8]</sup> who attributing this results to the major constituents of Echinacea; Caffeic acid derivatives which possess antioxidant and anti-inflammatory effects, and Alkamides which claimed to have stimulatory effects on the cells of the immune system.

American Indians were the first to use Echinacea, a plant native to central and southwestern America, for a variety of ailments such as cough, sore throat, and tonsillitis. Echinacea species include Echinacea purpurea, Echinacea pallida, and Echinacea angustifolia, which are commonly used to treat the common cold<sup>[22]</sup>

According to Ogal *et al.*,<sup>[17]</sup> findings strongly support the use of Echinacea for the long-term prevention of RTIs (respiratory tract infections), cold days, influenza and other enveloped virus infections, RTI complications, and antibiotic use in children aged 4 to 12.

Echinacea also inhibit the bacterial growth in rodents by increasing macrophages chemotaxis and the production of mediators as, IL-1 IL-6, IL-10 and TNF $\alpha$ <sup>[23]</sup>

According to Abdel-Naby Awad<sup>[8]</sup> AZT when combined to Echinacea didn't report hazardous interactions and the efficacy of both drugs were maintained.

Another herbal preparation made from the roots of pelargonium sidoides has been used for generations in South Africa to treat respiratory and gastrointestinal infections<sup>[14]</sup>

Pelargonium sidoides has positive effect upon innate and adaptive immunity and also possess anti-invasive and anti-adhesive probabilities as it prevents microbial adhesion to epithelial cells by attacking the bacterial adhesion molecules rather than those of the host tissues, so it is commonly used for prevention of bacterial and viral disease<sup>[24]</sup>

In the current study, the use of combination of Pelargonium sidoides extract and AZT as a prophylactic treatment showed a significant decrease in the number and severity of tonsillitis attacks when compared to the group receiving AZT alone.

According to our knowledge, there was no data in the previous literature on combination of AZT and Pelargonium sidoides in recurrent tonsillitis prophylaxis.

Observations from a study carried by Witte *et al* <sup>[25]</sup> suggested that Pelargonium sidoides acts as an immunostimulant, also, it promotes the innate immune defense and the ability of the body to eliminate microbes. Underlying mechanisms may be due to activation of phagocytes by TNF- $\alpha$ , induction of acute phase proteins and elevation of neutrophil production.

In a vitro study carried on group A-streptococci (GAS), pelargonium sidoides founded to reduce bacterial adherence to the epithelial cells, therefore, protects it from bacterial invasion and colony formation. The inhibition of group A streptococci invasion of epithelial cells protects the human from bacteria that may escape from immune system and antibiotic therapy, so it prevents chronicity<sup>[24]</sup>

When AZT was combined with Pelargonium sidoides or with Echinacea in this study; no interactions, adverse effects were reported and efficacy of the three drugs were maintained.

## CONCLUSION

The combination of Echinacea or Pelargonium sidoides with Azithromycin as a prophylactic therapy produced a significant reduction in number and severity of tonsillitis attacks in pediatrics superior to Azithromycin alone. We recommend more studies on using Echinacea or Pelargonium sidoides alone with different dosing schedules in prophylaxis of recurrent tonsillitis.

## REFERENCES

1. Cavalcanti VP, Camargo LA, Moura FS, Fernandes EJM, Lamaro-Cardoso J, Braga CADSB, *et al.* Staphylococcus aureus in tonsils of patients with recurrent tonsillitis: prevalence, susceptibility profile, and genotypic characterization. Braz J Infect Dis. 2019;23(1):8-14 <https://doi.org/10.1016/j.bjid.2018.12.003>.
2. Cottrell J, Yip J, Campisi P, Chadha NK, Damji A, Hong P, *et al.* Quality indicators for the diagnosis and management of pediatric tonsillitis. Int J Pediatr Otorhinolaryngol. 2020; 139:110441. <https://doi.org/10.1016/j.ijporl.2020.110441>.
3. Nemati S, Mohammad ghasemi F, Mojtahedi A, Habibi AF, Rouhi S, Leili EKN, *et al.* The effects of radiofrequency on the bacteriological and histological characteristics of tonsils in patients with chronic and persistent tonsillitis. Am J Otolaryngol. 2020; 41(6):102657. <https://doi.org/10.1016/j.amjoto.2020.102657>.
4. Popovych V, Koshel I, Malofichuk A, Pyletska L, Semeniuk A, Filippova O, *et al.* A randomized, open-label, multicenter, comparative study of therapeutic efficacy, safety and tolerability of BNO 1030 extract, containing marshmallow root, chamomile flowers, horsetail herb, walnut leaves, yarrow herb, oak bark, dandelion herb in the treatment of acute non-bacterial tonsillitis in children aged 6 to 18 years. Am J Otolaryngol. 2019;40(2):265-273. <https://doi.org/10.1016/j.amjoto.2018.10.012>.
5. Galli J, Calò L, Pošteraro B, Rossi G, Sterbini FP, Paludetti G, *et al.* Pediatric oropharyngeal microbiome: Mapping in chronic tonsillitis and tonsillar hypertrophy. Int J Pediatr Otorhinolaryngol. 2020; 139:110478. <https://doi.org/10.1016/j.ijporl.2020.110478>. Epub 2020 Nov 3. PMID: 33160244.
6. Norton L, Myers A. The treatment of streptococcal tonsillitis/pharyngitis in young children. World J Otorhinolaryngol Head Neck Surg. 2021; (3):161-165. <https://doi.org/10.1016/j.wjorl.2021.05.005>. PMID: 34430823; PMCID: PMC8356196.

7. Heward E, Rocke J, Kumar N, Izzat S. Recurrent tonsillitis and parental perceptions of tonsillectomy during the COVID-19 pandemic. *Int J Pediatr Otorhinolaryngol.* 2020; 139:110463. <https://doi.org/10.1016/j.ijporl.2020.110463>.
8. Abdel-Naby Awad OG. Echinacea can help with Azithromycin in prevention of recurrent tonsillitis in children. *Am J Otolaryngol.* 2020; 41(4):102344. <https://doi.org/10.1016/j.amjoto.2019.102344>.
9. Patel SD, Daher GS, Engle L, Zhu J, Slonimsky G. Adult tonsillectomy: An evaluation of indications and complications. *Am J Otolaryngol.* 2022; 43(3): 103403. <https://doi.org/10.1016/j.amjoto.2022.103403>.
10. Abdel-Naby Awad OG. Prevalence of humoral immunodeficiency in adult patients with recurrent tonsillitis. *Am J Otolaryngol.* 2019; 40(6):102275. <https://doi.org/10.1016/j.amjoto.2019.08.006>. Epub 2019 Aug 13. PMID: 31445931.
11. El Hennawi DED, Geneid A, Zaher S, Ahmed MR. Management of recurrent tonsillitis in children. *Am J Otolaryngol.* 2017; 38(4):371-374 <https://doi.org/10.1016/j.amjoto.2017.03.001>. Gopal R, Harikrishnan S, Sivasankaran S, Ajithkumar VK, Titus T, Tharakan JM. Once weekly azithromycin in secondary prevention of rheumatic fever. *Indian Heart J.* 2012; 64(1):12-5. [https://doi.org/10.1016/S0019-4832\(12\)60004-2](https://doi.org/10.1016/S0019-4832(12)60004-2).
12. Ogal M, Johnston SL, Klein P, Schoop R. Echinacea reduces antibiotic usage in children through respiratory tract infection prevention: a randomized, blinded, controlled clinical trial. *Eur J Med Res.* 2021; 26(1):33. <https://doi.org/10.1186/s40001-021-00499-6>.
13. Goel V, Chang C, Slama J, Barton R, Bauer R, Gahler R, *et al.* Echinacea stimulates macrophage function in the lung and spleen of normal rats. *J Nutr Biochem.* 2002; 13(8):487. [https://doi.org/10.1016/s0955-2863\(02\)00190-0](https://doi.org/10.1016/s0955-2863(02)00190-0). PMID: 12165361.
14. Currier NL, Miller SC. Echinacea purpurea and melatonin augment natural-killer cells in leukemic mice and prolong life span. *J Altern Complement Med.* 2001; 7(3):241-51. <https://doi.org/10.1089/107555301300328115>. PMID: 11439845.
15. von Rosensteil NA, Adam D. Macrolide antibacterials, Drug interactions of clinical significance. *Drug Saf.* 1995; 13(2):105-22. <https://doi.org/10.2165/00002018-199513020-00005>. PMID: 7576262.
16. Kamin W, Funk P, Seifert G, Zimmermann A, Lehmacher W. EPs 7630 is effective and safe in children under 6 years with acute respiratory tract infections: clinical studies revisited. *Curr Med Res Opin.* 2018; 34(3):475-485. <https://doi.org/10.1080/03007995.2017.1402754>. Epub 2017 Dec 8. PMID: 29119837.
17. Brendler T, van Wyk BE. A historical, scientific and commercial perspective on the medicinal use of *Pelargonium sidoides* (Geraniaceae). *J Ethnopharmacol.* 2008; 119(3):420-33. <https://doi.org/10.1016/j.jep.2008.07.037>. Epub 2008 Aug 3. PMID: 18725280.
18. Theisen LL, Muller CP. EPs® 7630 (Umckaloabo®), an extract from *Pelargonium sidoides* roots, exerts anti-influenza virus activity in vitro and in vivo. *Antiviral Res.* 2012; 94(2):147- 56. <https://doi.org/10.1016/j.antiviral.2012.03.006>. Epub 2012 Mar 28. PMID: 22475498.
19. Brandtzaeg P. Immunology of tonsils and adenoids: everything the ENT surgeon needs to know. *Int J Pediatr Otorhinolaryngol.* 2003; 67:S69:S76. <https://doi.org/10.1016/j.ijporl.2003.08.018>.
20. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biol Psychiatry.* 2004; 57:788–92. <https://doi.org/10.1016/j.biopsych.2004.12.035>.
21. Schotz K, Noldner M. Mass spectroscopic characterization of oligomeric proanthocyanidins derived from an extract of *Pelargonium sidoides* roots (EPs 7630) and pharmacological screening in CNS models. *Phytomedicine.* 2007; 14(6):32–39. <https://doi.org/10.1016/j.phymed.2006.11.019>.
22. Steinmüller C, Roesler J, Gröttrup E, Franke G, Wagner H, Lohmann-Matthes ML. Polysaccharides isolated from plant cell cultures of *Echinacea purpurea* enhance the resistance of immunosuppressed mice against systemic infections with *Candida albicans* and *Listeria monocytogenes*. *Int J Immunopharmacol.* 1993; 15(5):605-14. [https://doi.org/10.1016/0192-0561\(93\)90078-d](https://doi.org/10.1016/0192-0561(93)90078-d). PMID: 8375943.
23. Conrad A, Jung I, Tioua D, Lallemand C, Carrapatoso F, Engels I, *et al.* Extract of *Pelargonium sidoides* (EPs 7630) inhibits the interactions of group A-streptococci and host epithelia in vitro. *Phytomedicine* 14 Suppl. 2007; 6:52-9. <https://doi.org/10.1016/j.phymed.2006.11.018>. Epub 2006.
24. Witte K, Koch E, Volk HD, Wolk K, Sabat R. The *Pelargonium sidoides* Extract EPs 7630 Drives the Innate Immune Defense by Activating Selected MAP Kinase Pathways in Human Monocytes. *PLoS One.* 2015; 10(9):e0138075. <http://doi.org/10.1371/journal.pone.0138075>.