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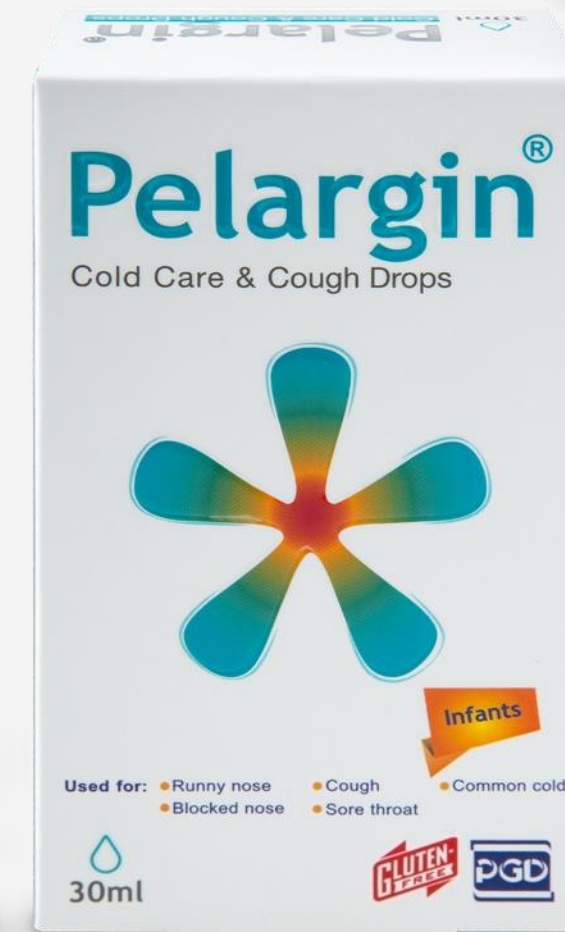


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**SUSTAINABLY SOURCED &
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INTRODUCING PELARGONIUM SIDIODES™

Our flagship herb, Pelargonium sidoides, is a plant that has significant commercial and healing potential in the world of natural cold and flu phytomedicines.

Our sustainably sourced raw material of Pelargonium sidoides is a perfect ingredient in cold and flu products for natural pharmaceutical and health product manufacturers.

PROVEN BENEFITS

- The raw material with the highest and best quality is prepared from South Africa
- Exclusive agency of Afrigetics Botanicals in Iran
- North and central America / Europe / Asia and Asia Pacific / Africa and Near East

ASSERTS & EXPECTATIONS OF EPS 7630

- Bacteriostatic
- Virostatic Agent
- Immunomodulatory Agent
- Anti-inflammatory and Congestion
- Good taste
- Common cold symptoms suppresor
- Reducing the duration of cold
- High safety and no side effects = TD50% 2000mg/kg
- non-hypnotic



29 September 2015
EMA/HMPC/444251/2015
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Pelargonium sidoides* DC and/or
Pelargonium reniforme Curt., radix

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Draft - revision

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Pelargonium sidoides</i> DC and/or <i>Pelargonium reniforme</i> Curt., radix
Herbal preparation(s)	Liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m) Dry extract, (DER 4-25:1), extraction solvent ethanol 11% (m/m)
Pharmaceutical form(s)	Herbal preparations in liquid or solid dosage forms for oral use.
Rapporteur	Z. Biró-Sándor

•**Toxicity Profile and LD₅₀ of Pelargonium sidoides Extract**

•According to toxicological data from **the European Medicines Agency (EMA Herbal Monograph, 2021)**, the **WHO monographs on African medicinal plants**, and peer-reviewed Q1 journals such as Phytomedicine and Toxicology Reports, the root extract of Pelargonium sidoides demonstrates an excellent safety profile.

•**Experimental Toxicology Findings**

Animal Model	Administration Route	Reported LD ₅₀	Remarks
Rat	Oral	>5000 mg/kg	No systemic toxicity or mortality observed
Mouse	Oral	≈3500–5000 mg/kg	Only transient hypoactivity at high doses
Rat	Intraperitoneal	>1000 mg/kg	Mild gastrointestinal signs at toxic range

In all standardized OECD toxicity protocols, no lethal dose could be accurately determined because even at oral doses of 5 g/kg, animals survived without major toxic effects. Consequently, the extract is categorized as “**Practically Non-Toxic**” in conventional toxicological classification.

specification of extract (EPS 7630)

Antibacterial properties against resistant strains of *Staphylococcus aureus*

TNF - IL1 - IL2 Optimal Performance Setting

Interferon-like effects

Mucolytic agents: break peptide, glycosidic, and disulfide bonds in mucus, reducing its viscosity and facilitating clearance.

Suppl. Table 1. Effective antibacterial concentrations of EPs 7630, other *Pelargonium sidoides* root extracts, and their ingredients.

Assay	Extract (ingredient)	Bacterial strain	Activity	Reference
Agar dilution method	<i>Pelargonium sidoides</i> crude root extract	<i>Escherichia coli</i> ATCC 25922	5 mg/mL MIC ¹	Kayser and Kolodziej, 1997
	<i>Pelargonium sidoides</i> crude root extract	<i>Klebsiella pneumoniae</i> V 6089	7.5 mg/mL MIC	Kayser and Kolodziej, 1997
	<i>Pelargonium sidoides</i> crude root extract	<i>Proteus mirabilis</i> ATCC 14153	5 mg/mL MIC	Kayser and Kolodziej, 1997
	<i>Pelargonium sidoides</i> crude root extract	<i>Pseudomonas aeruginosa</i> ATCC 27853	5 mg/mL MIC	Kayser and Kolodziej, 1997
	<i>Pelargonium sidoides</i> crude root extract	<i>Haemophilus influenzae</i> ATCC 33379	5 mg/mL MIC	Kayser and Kolodziej, 1997
	<i>Pelargonium sidoides</i> crude root extract	<i>Staphylococcus aureus</i> ATCC 25923	7.5 mg/mL MIC	Kayser and Kolodziej, 1997
	<i>Pelargonium sidoides</i> crude root extract	Beta-hemolytic <i>Streptococcus</i> 1451	7.5 mg/mL MIC	Kayser and Kolodziej, 1997
	<i>Pelargonium sidoides</i> crude root extract	<i>Streptococcus pneumoniae</i> (strain 78)	7.5 mg/mL MIC	Kayser and Kolodziej, 1997
Agar dilution method	EPs 7630	<i>Klebsiella pneumoniae</i> V 6089	13.8 mg/mL MIC	Kolodziej et al., 2003
	EPs 7630	<i>Escherichia coli</i> ATCC 25922	>13.8 mg/mL MIC	Kolodziej et al., 2003
	EPs 7630	<i>Pseudomonas aeruginosa</i> ATCC 27853	>13.8 mg/mL MIC	Kolodziej et al., 2003

The efficacy of *Pelargonium sidoides* in the treatment of upper respiratory tract infections in children with transient hypogammaglobulinemia of infancy

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ARTICLE INFO

Keywords:

Child
Herbal medicine
Pelargonium sidoides
Transient hypogammaglobulinemia of infancy
Upper respiratory tract infections

ABSTRACT

Transient hypogammaglobulinemia of infancy (THI), defined as prolongation of physiological hypogammaglobulinemia normally seen between the initial 3rd and 6th months of life, is one of the most common immune deficiencies of childhood. Recurrent upper respiratory tract infections (URTI) are rather common in this group of patients, and generally, antibiotic treatment is the usual choice, although viruses involved in most cases. *Pelargonium sidoides* extract a herbal drug with known immunomodulator, antiviral and antibacterial effects. In this randomized, placebo controlled, prospective, monocentric pilot study, 14 of 28 patients with a diagnosed THI, were given *Pelargonium sidoides*, while 14 were given placebo during the period of URTI. Before and after the treatment period of one week, complete blood count, prothrombin time, activated prothromboplastin time, serum alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transpeptidase, total and direct bilirubin levels were measured. Mothers were asked to fill in a questionnaire for the recovery of the clinical symptoms during the treatment. The results were evaluated and compared in both group to assess the effect of *Pelargonium sidoides*. As a conclusion, the *Pelargonium sidoides* group showed increased appetite. The *Pelargonium sidoides* were found to be beneficial for the nasal congestion, recovery of daily and nocturnal cough but not found to be significant. Further studies with large number of participants are necessary to highlight the effect of *Pelargonium sidoides* in children with transient hypogammaglobulinemia of infancy.

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Introduction

The concept of Transient Hypogammaglobulinemia was firstly announced to the English medical literature by Gitlin and Janeway (1956). Transient hypogammaglobulinemia of infancy (THI) is defined as a prolongation of the physiological hypogammaglobulinemia period when maternal immunoglobulin (Ig) levels start to decline and the infant starts to synthesize his own Ig's between the initial 3rd and 6th months of the life, the criteria needed for diagnosis of this disorder have not yet been standardized. Its incidence is not fully and exactly known, and its incidence does not differ by the sex (Keles et al. 2010). Though causes underlying THI are not exactly known either, a delay in maturation of B cells, and helper T-cell (CD4) maturation/development disorders, and disorders in interplay and relationship between cytokines, all as detected by pathological means, are suggested among the probable underlying reasons. Recurrent upper respiratory tract infections (URTI) are rather common in this disease. It is reported that normal Ig levels are reached between ages 2 and 5 years in most of the patients with

THI, which is a self-limiting disease (Doğu et al. 2004; Karaca et al. 2010; Keles et al. 2010; Kiliç et al. 2000).

Historically, *Pelargonium sidoides* has been used by African indigenous tribes to treat various disorders such as gastrointestinal disorders and respiratory tract infections. The colonization of South Africa by the Dutch and British in 17th century, the effect of this herbal drug was also noticed by the Europeans, and the interest shown in this herbal drug increased after Colonel Charles Stevens personally used and benefitted from it (Brendler and van Wyk 2008; Kolodziej and Schulz 2003). Thereafter, a proprietary extract of the roots of *Pelargonium sidoides*, EPs® 7630, was emerged as a modern phyto-pharmaceutical drug after extensive research. EPs® 7630 has been proven to have antiviral, antibacterial and immunomodulatory and secretomotoric effects and is used in modern medicine in the treatment of respiratory tract infections such as acute bronchitis, sinusitis and the common cold (Brendler and van Wyk 2008; Haidvogel et al. 1996; Haidvogel and Heger 2007).

We aimed and planned to conduct a randomized, placebo-

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Materials and methods

This double-blinded and monocentric pilot study was conducted with 28 patients suffering from URTI complicated with THI at Erciyes University, Faculty of Medicine, Department of Pediatric Immunology between September 2007 and April 2009. The study was approved by the 01/368 numbered, 07.11.2006 dated decision of Erciyes University Ethics Committee. In addition the study was carried out after obtaining a written informed consent from all parents of the subjects. The study followed the guidelines of the Declaration of Helsinki and Tokyo for the enrolled subjects.

Plant material

EPs® 7630 is a herbal drug preparation from the roots of *Pelargonium sidoides* (1:8–10); extraction solvent:ethanol 11% (w/w) (Schoetz et al. 2008) and was kindly provided by Dr. Willmar Schwabe GmbH & Co. KG., Karlsruhe, Germany.

Inclusion criteria of patients

- (1) Diagnosis of THI
- (2) Patients suffering from acute URTI symptoms
- (3) age between 6 months to 5 years,
- (4) Normal values of complete blood count, prothrombin time (PT), activated prothromboplastin time (aPTT), serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), total and direct bilirubin
- (5) Tuberculosis skin test (PPD skin test) result of 5–10 mm (+),
- (6) Negative result in STREP test

Patients who did not conform to the above listed criteria, and patients with elevated average white blood cell count and/or high CRP values indicative of a bacterial infection were excluded from the study. Patients using any other medication were also excluded.

Study plan

All patients admitted with symptoms of URTI (cough, nasal draining, fever, etc.) first underwent a STREP test in order to exclude

Table 1
Scale of the symptom score.

General state of health	Good	0
	Poor	1
Nasal congestion	Absent	0
	Present	1
Appetite	Absent	0
	Present	1
Daily cough frequency	Absent	0
	Present	1
Nocturnal cough frequency	Absent	0
	Present	1
Fever	<38 °C	0
	>38 °C	1
Pain	Absent	0
	Present	1
Sleep pattern	Normal	0
	Bad	1
Additional symptoms including dyspnea, vomiting, chest pain	Absent	0
	Present	1

Statistical method

Study results for categorical parameters are presented by means of absolute and relative frequencies, Fisher's exact test, chi-square test was employed to compare the two groups of patients, and the tests of McNemar and Bowker, respectively, were applied for the comparison between days 1 and 7 within both groups. Metrical data like the age are presented by median and range, the Mann–Whitney U-test was used to compare the treatment groups. All calculations were performed with a statistical software-package named "SPSS for Windows, Version 16.0, SPSS Inc., USA".

Results

Of the 28 patients enrolled to the study, 20 (71.4%) were boys, and 8 (28.6%) were girls. The age range of patients in both groups was between 6 and 60 months, and their average median age was 30.14 months. *Pelargonium sidoides* extract was administered to 11 (78.5%) boys and 3 (21.5%) girls, while placebo was given to 9 (64.2%) boys and 5 (35.8%) girls. We did not notice any incompliance by the measure of returned empty bottles.

The two groups were compared in terms of average white blood cell count, platelet count, hemoglobin level, and serum AST, ALT, GGT, total bilirubin, direct bilirubin, PT/aPTT and INR levels, and no

comparison between the 1st and 7th day separately in both groups revealed no significant difference in terms of improvement of general status of health, reduction of fever and pain between 1st and 7th day in the *Pelargonium sidoides* group.

Discussion

Pelargonium sidoides has a long healing tradition in South African folk medicine where it has been used to treat various infections. The modern extract EPs® 7630 derived from the roots of *Pelargonium sidoides*, has been shown to have immunomodulatory, antiviral, antibacterial and secretomotoric effects (Brendler and van Wyk 2008; Haidvogel and Heger 2007; Matthys and Heger 2006, 2007). This extract is currently used worldwide for the treatment of acute respiratory tract infections where antibiotic use is unnecessary (Timmer et al. 2008). In some studies, it is reported that rates of side effects associated with use of antibiotics are higher than the rates of side effects associated with the use of *Pelargonium sidoides* (Bent et al. 1999; Fahey et al. 1998). There are many adult and children studies proving the efficiency of *Pelargonium sidoides* extract in treatment of bronchitis. Among others these studies have clearly demonstrated that *Pelargonium sidoides* extract is more efficient than placebo in reduction of cough frequency (Chuchalin et al. 2005; Kamin et al. 2010a,b; Matthys et al. 2003, 2010; Matthys and Heger 2007). Consistent with the medical literature, our pilot study also indicated a reduction in daily and nocturnal cough frequency but the p values were under the level of significance.

Nasal congestion and draining are the most common seen initial symptoms of upper respiratory tract infections. A study conducted by Lizogub et al. (2007) on 103 common cold patients revealed that the extent of nasal congestion decreases faster in the *Pelargonium sidoides* group compared to the placebo group. In our pilot study, we also observed that nasal congestion symptoms diminished in most of the patients in the *Pelargonium* group but increased in the placebo group.

Behavioral changes may be observed in patients during infection periods. Particularly in children, lack of appetite (anorexia) and low spirits are common findings. A rat study revealed that *Pelargonium sidoides* helped in relieving anorexia in rats (Nöldner and Schötz 2007). In another study, it was shown that the anorexia (lack of appetite) symptom improved by approximately 80% in the initial 3 days in 259 patients under *Pelargonium sidoides* treatment (Dome and Schuster 1996). In our study, appetite, being one of the best representative factors in terms of indicating the general state of

Variations in white blood cell, hemoglobin and platelet counts or elevation in liver enzymes may be observed in association with bone marrow suppression as a result of use of medical drugs. Loew and Koch (2008) demonstrated that coumarine derivatives contained in *Pelargonium sidoides* do not have any hepatotoxic effect. In our study, we did not find any significant difference in liver enzymes and CBC values between pre-treatment and post-treatment results either; neither in the *Pelargonium sidoides* group nor in placebo group.

The probability of increase in treatment-associated bleeding risk comes to mind due to presence of coumarines in basic ingredients of *Pelargonium sidoides*. Studies conducted by Chuchalin et al. and Koch et al. indicated no effect of *Pelargonium sidoides* on PT, PTT values. This is associated with the non-anticoagulant character of coumarine derivatives contained (Chuchalin et al. 2005; Koch and Biber 2007). In our study, consistent with the medical literature, we did not detect any significant difference between the pre-treatment and the post-treatment PT, PTT values in the *Pelargonium sidoides* group either.

Many studies have been conducted about adverse reactions or side effects of *Pelargonium sidoides* extract since it was introduced to market. As a part of the pharmacological monitoring program of WHO, de Boer et al. (2007) reported a total of 34 allergic reaction cases, a great many of which may be related to German-origin *Pelargonium sidoides* extracts. However, Matthys and Köhler (2010) recently had systematically reviewed the safety profile of *Pelargonium sidoides* extract EPs 7630 based upon 25 clinical trials and post-marketing surveillance studies with a total of more than 9000 patients – including pediatric safety with about 4000 children and adolescents – and reported a good tolerability and no serious adverse drug reactions. Our study did also not reveal any severe side effects in any of the patients.

As a conclusion, it is noted that all studies reported in the medical literature have been conducted during infection periods in normally healthy subjects with no underlying disease, and that *Pelargonium sidoides* is fairly effective in treatment of these infections. In our study, which was conducted during URTI, of patients suffering from THI, an increase in appetite and, close-significant reduction of nasal congestion were detected. In addition, the symptoms of cough frequency, fever, pain, sleep pattern, and general state of health in the *Pelargonium sidoides* group were improved; but the results of these symptoms were under the level of significance. The major limitation of our study design is the limited number of the patients which does not allow making confirmatory

In patients with transient hypogammaglobulinemia of infancy (THI) accompanied by upper respiratory tract infection (URTI),

treatment with **EPs® 7630 (*Pelargonium sidoides*)** led to a notable improvement in appetite and a **near-significant reduction in nasal symptoms**.

Other clinical parameters – including **cough, fever, pain, and sleep** quality – showed a trend toward improvement but did not reach statistical significance.

The extract demonstrated **high safety, with no adverse effects on liver enzymes or coagulation profiles**.

The main limitation of the study was the **small sample size**, which restricts definitive conclusions.



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Phytomedicine 14 (2007) SVI 69–73

Phytomedicine

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***Pelargonium sidoides* preparation (EPs[®] 7630) in the treatment of acute bronchitis in adults and children[☆]**

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Pelargonium sidoides preparation (EPs[®] 7630) in the treatment of acute bronchitis in adults and children[☆]

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Abstract

Acute bronchitis, although mostly caused by viral infections, is commonly treated with antibiotics. As antibiotics should only be prescribed upon strict indication, treatment options like a liquid herbal drug preparation from the roots of *Pelargonium sidoides* (EPs[®] 7630) gain more and more interest.

To evaluate the efficacy and safety of treatment with EPs[®] 7630 in patients with acute bronchitis, a multi-centre, prospective, open observational study was conducted in 440 study sites located in Germany. A total of 2099 patients aged 0–93 years with productive cough for less than six days without indication for treatment with antibiotics were given EPs[®] 7630-solution in an age-dependent dosage for 14 days. The primary outcome criterion was the mean change of the Bronchitis Severity Score (BSS: cough, sputum, rales/rhonchi, chest pain at cough, dyspnoea) from baseline to patient's individual last observation.

During treatment, the mean BSS of all patients decreased from 7.1 ± 2.9 points at baseline to 1.0 ± 1.9 points at patients' individual last visit. Subgroup analysis for children showed a decrease of mean BSS from 6.3 ± 2.8 points to 0.9 ± 1.8 points and analysis of children younger than three years showed a decrease of mean BSS from 5.2 ± 2.5 points to 1.2 ± 2.1 points. Adverse events occurred in 26/2099 (1.2%) patients. Serious adverse events were not reported.

In conclusion, EPs[®] 7630 is an effective and well tolerated treatment of acute bronchitis in adults, children and infants outside the strict indication for antibiotic treatment.

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Keywords: Acute bronchitis; Children; Herbal medicine; Bronchitis severity score; EPs[®] 7630; Umckaloabo[®]

Introduction

Acute bronchitis is defined as a lower respiratory tract infection and is one of the most common diagnoses

made by primary care physicians (Knutson and Braun, 2002). Although in up to 95% of cases the cause is viral, acute bronchitis has traditionally been treated with antibiotics (Hueston and Mainous, 1998). Because of increasing concern about antibiotic resistance and the

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infants.

Discussion

The results of this study showed good efficacy and safety of EPs[®] 7630-solution in the treatment of children, infants and adults with acute bronchitis.

The BSS of all patients decreased from a median of 7 points at baseline to a median of 0 points at the third follow-up, corresponding to an average decrease of median 6 points. Subgroup analyses for children and infants show similar results. Complete recovery or major improvement was documented in 94.2% of all patients.

Bronchitis specific symptoms showed remission rates above 80% for all patients except for the symptom cough, which showed a remission rate of 59.7%. This is in line with previous findings that cough can last for two weeks or more in 26% of patients (Chesnutt et al., 2002). Further symptoms like hoarseness and headache showed

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Clinical Overview – Matthys et al. 2007 (Phytomedicine)

Study Summary: Matthys et al., 2007 – Phytomedicine

Efficacy and safety of EPs® 7630 in the treatment of acute bronchitis in adults and children.

Summary:

A multicenter, prospective, open-label observational study conducted at 440 sites in Germany included 2,099 patients aged 0–93 years with acute bronchitis and productive cough for less than six days.

Patients received age-adjusted doses of EPs® 7630 oral solution for 14 days.

The mean Bronchitis Severity Score (BSS) improved significantly from 7.1 ± 2.9 to 1.0 ± 1.9 .

Adverse events occurred in only 1.2% of participants—none serious.

Conclusion: EPs® 7630 is a safe, well-tolerated, and effective therapy for acute bronchitis across all age groups and represents a rational alternative to antibiotics when bacterial infection is not indicated.

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Review

Antimicrobial, Antiviral and Immunomodulatory Activity Studies of *Pelargonium sidoides* (EPs[®] 7630) in the Context of Health Promotion

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Received: 30 August 2011; in revised form: 20 September 2011 / Accepted: 29 September 2011 / Published: 10 October 2011

Abstract: *Pelargonium* species contribute significantly to the health care of a large population in the Southern African region, as part of a long-standing medical system intimately linked to traditional healing practices. Most notably, extracts of the roots of *P. sidoides* have commonly been applied for the treatment of dysentery and diarrhoea but only occasionally for respiratory complaints. Clinical trials have shown that a modern aqueous-ethanolic formulation of *P. sidoides* extracts (EPs[®] 7630) is an efficacious treatment for disorders of the respiratory tract, for example bronchitis and sinusitis. It should be noted that EPs[®] 7630 is the most widely investigated extract and therefore is the

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Abstract: *Pelargonium* species contribute significantly to the health care of a large population in the Southern African region, as part of a long-standing medical system intimately linked to traditional healing practices. Most notably, extracts of the roots of *P. sidoides* have commonly been applied for the treatment of dysentery and diarrhoea but only occasionally for respiratory complaints. Clinical trials have shown that a modern aqueous-ethanolic formulation of *P. sidoides* extracts (EPs[®] 7630) is an efficacious treatment for disorders of the respiratory tract, for example bronchitis and sinusitis. It should be noted that EPs[®] 7630 is the most widely investigated extract and therefore is the focus of this review. In order to provide a rationale for its therapeutic activity extracts have been evaluated for antibacterial activity and for their effects on non-specific immune functions. Only moderate direct antibacterial capabilities against a spectrum of bacteria, including *Mycobacteria* strains, have been noted. In contrast, a large body of *in vitro* studies has provided convincing evidence for an anti-infective principle associated with activation of the non-specific immune system. Interestingly, significant inhibition of interaction between bacteria and host cells, a key to the pathogenesis of respiratory tract infections, has emerged from recent studies. In addition, antiviral effects have been demonstrated, including inhibition of the replication of respiratory viruses and the enzymes haemagglutinin and neuraminidase. Besides, an increase of ciliary beat frequency of respiratory cells may contribute to the beneficial effects of *P. sidoides* extracts. This example provides a compelling argument for continuing the exploration of Nature and traditional medical systems as a source of therapeutically useful herbal medicines.

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residing mycobacteria. Although this still remains to be demonstrated, the present data provide a clue for the claimed efficacy of this herbal medicine in the earlier treatment of tuberculosis and related diseases in traditional medicine. Interestingly, when tested against macrophages as a mammalian host cell control, all samples revealed no or only moderate cytotoxicity.

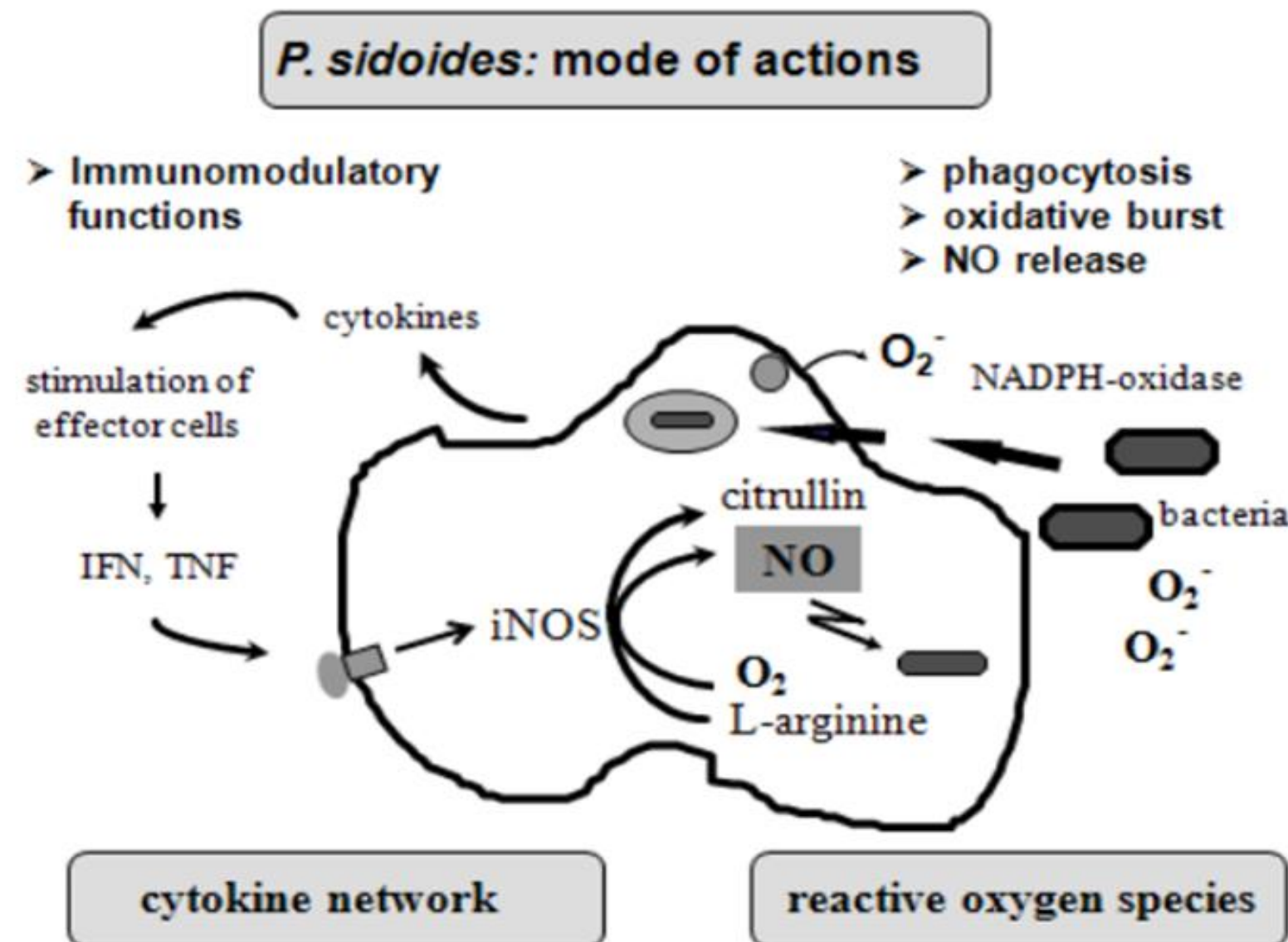
2.6.3. Induction of the Release of Tumour Necrosis Factor, IL-1 and IL-12

Macrophage activation usually is a polyphenotypic event, with TNF release during the early response to infection [54]. Measurement of TNF-activity induced by the above mentioned *Pelargonium* extracts was therefore another important immunological parameter in the evaluation of the anti-infective potential of this herbal medicine. Initially, TNF-release was assessed in a functional assay [66], in which TNF-sensitive ML929F treated with supernatants of sample-activated BMM Φ were rapidly

lysed in its presence. Surviving cells incorporate crystal violet dye and their relative number was spectrophotometrically determined. At the concentration of ≤ 25 $\mu\text{g/mL}$, the ethyl acetate (*ca.* 20 U/mL) and the *n*-butanol phase (*ca.* 19 U/mL) were found to possess a moderate TNF-inducing potential. All remaining samples showed only a negligible effect (< 5 U/mL) compared to the LPS stimulus (10 ng/mL; 184 U/mL) as positive control [60]. Having in mind that systemic TNF can be fatal the moderate TNF-inducing capability of the *Pelargonium* extracts in non-infected cells may be beneficial. This functional bioassay has hitherto not been extended to infected macrophages. However, gene expression analysis clearly showed augmented and prolonged up-regulation of TNF- α transcripts in infected cells (*vide supra*). Confirmatory evidence of increased intracellular TNF- α levels induced by

detected in *P. sidoides* based medicines. A simplified overview of induced cytotoxic defence mechanisms is shown in Figure 3.

Figure 3. Simplified illustration of cytotoxic defence mechanisms of activated macrophages induced by the root extract of *P. sidoides*.



The extract of Pelargonium sidoides activates macrophages, stimulating the secretion of cytokines such as IFN and TNF, induction of iNOS, and the production of nitric oxide and reactive oxygen species. These processes collectively enhance phagocytosis, oxidative burst, and the destruction of microorganisms.

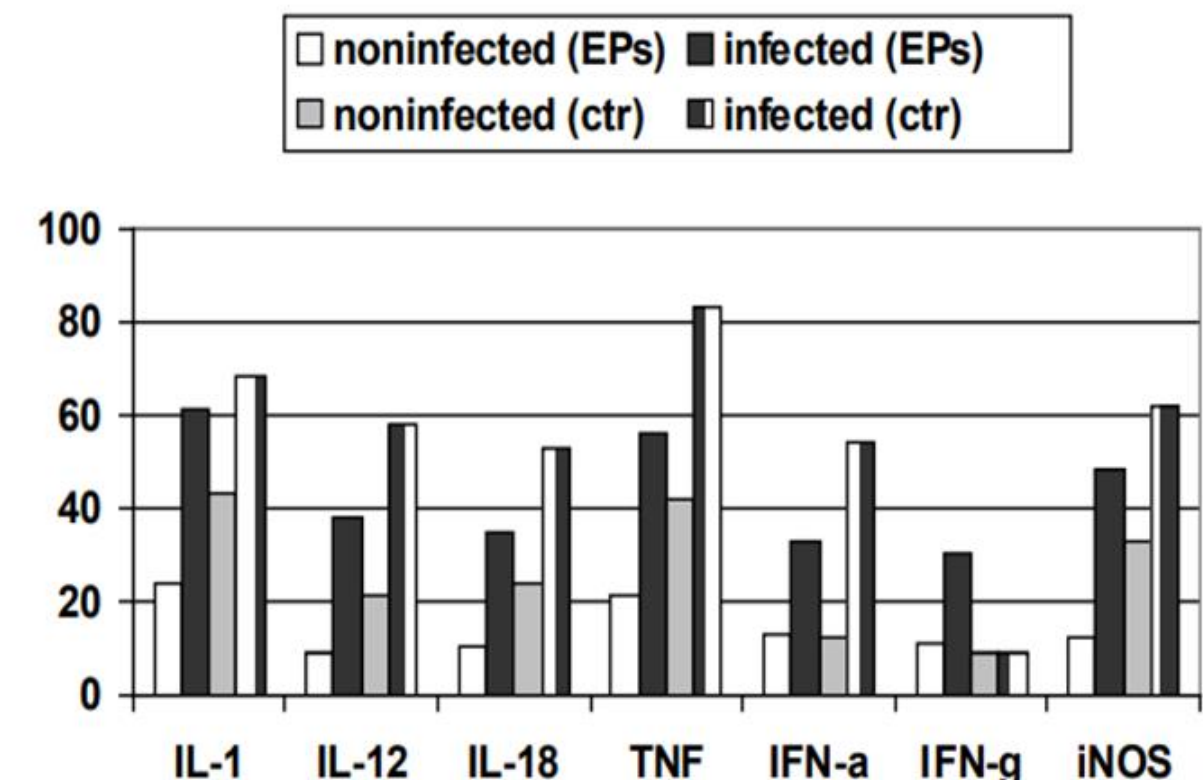
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This chart illustrates the expression of cytokine genes IL-1, IL-12, IL-18, TNF, IFN- α , IFN- γ , and iNOS in RAW 264.7 macrophages stimulated with the EPs® 7630 extract. In macrophages infected with *Leishmania major*, treatment with EPs® 7630 significantly increases iNOS expression and Th1-related cytokines, particularly IL-12 and IFN- γ . This indicates macrophage activation and enhancement of antimicrobial immunity—an effect comparable to classical stimulants such as LPS/IFN- γ .

Pelargonium sidoides enhances innate and cellular immunity against bacterial, viral, and parasitic infections through controlled activation of macrophages, increased secretion of defensive cytokines, and induction of nitric oxide (NO) production. At the same time, it prevents excessive inflammation, thereby protecting tissues from damage and oxidative stress.

observed at functional levels (*vide supra*). Interestingly, this herbal medicine also stimulated infected cells to produce IFN- γ transcripts. The expression of IFN- γ itself in cells of monocytic lineage has merely been noted under certain physiological and pathological conditions [71,72]. Also worthy of mention is the up-regulation of IL-12 and IL-18 mRNA levels in that both cytokines are critical to host defence against a variety of pathogens and are involved in the production of IFN- γ [73,74]. Subsequent studies suggested that IFN- γ mRNA expression appeared to be a unique feature of *P. sidoides* among herbal extracts [75]. The gene expression experiments thus provided evidence for macrophage activation at the transcriptional level.

Figure 5. Expression of iNOS and cytokine transcripts in non-infected and in *L. major* infected RAW 264.7 cells stimulated for 4 h with 50 μ g/mL of EPs® 7630 and LPS/IFN- γ as positive control (ctr). Results are shown relative to hypoxanthine-guanine-phosphoribosyl transferase mRNA, defined as 100%.



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Cleans and protects

Clinical Efficacy
and Safety of Xylitol-Based
Intranasal Spray **(OCHI)**
in Pediatric Airway Health





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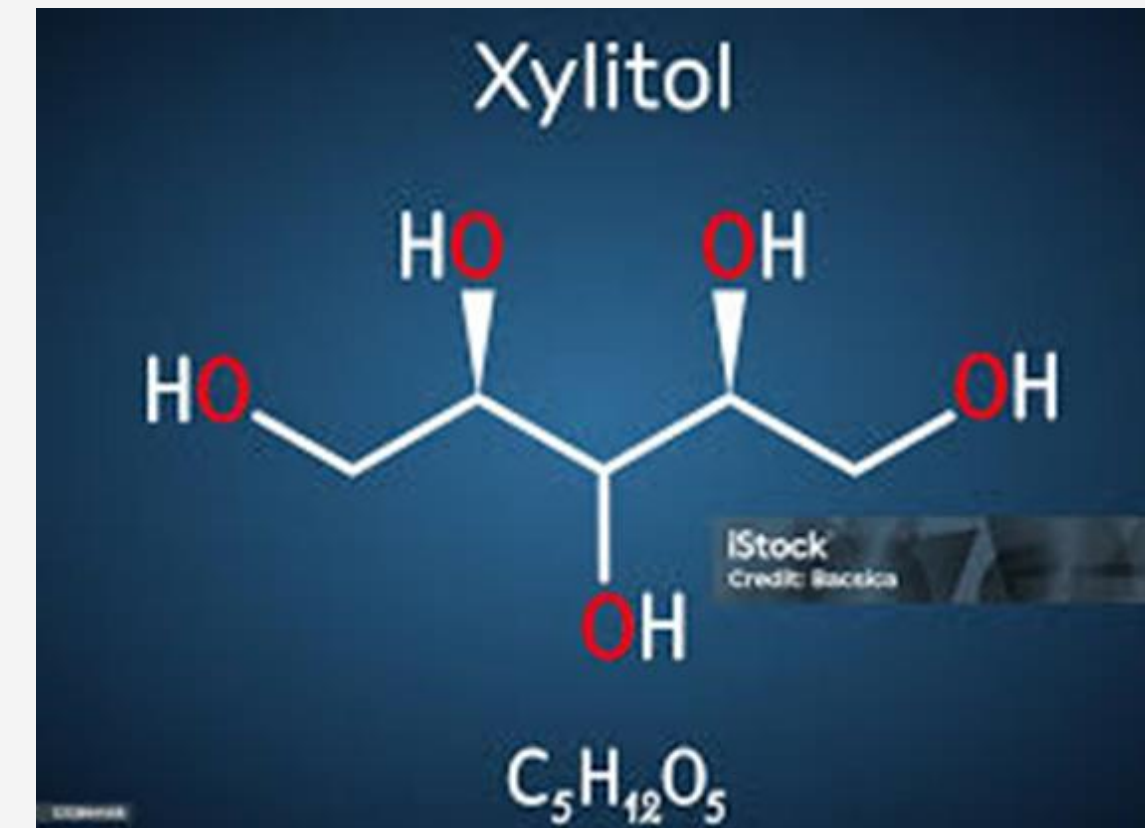
- product based on: **xylitol**
- Designed to: preserve **upper respiratory tract health** in both children and adults
- Exhibits three simultaneous effects: **antibacterial, antiviral, and anti-inflammatory**
- **Free from decongestants, non-habit-forming, and safe for long-term use**



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What Is Xylitol?

- Xylitol is a **five-carbon sugar alcohol (C₅H₁₂O₅)** belonging to the **pentitol** group
- Naturally found in fruits and vegetables (e.g., raspberries, corn)
- Key properties: **non-fermentable, hypo-osmolar**, and **biocompatible** with mucosal tissues
- Possesses unique ability to **retain moisture, reduce inflammation, and inhibit microbial adhesion**

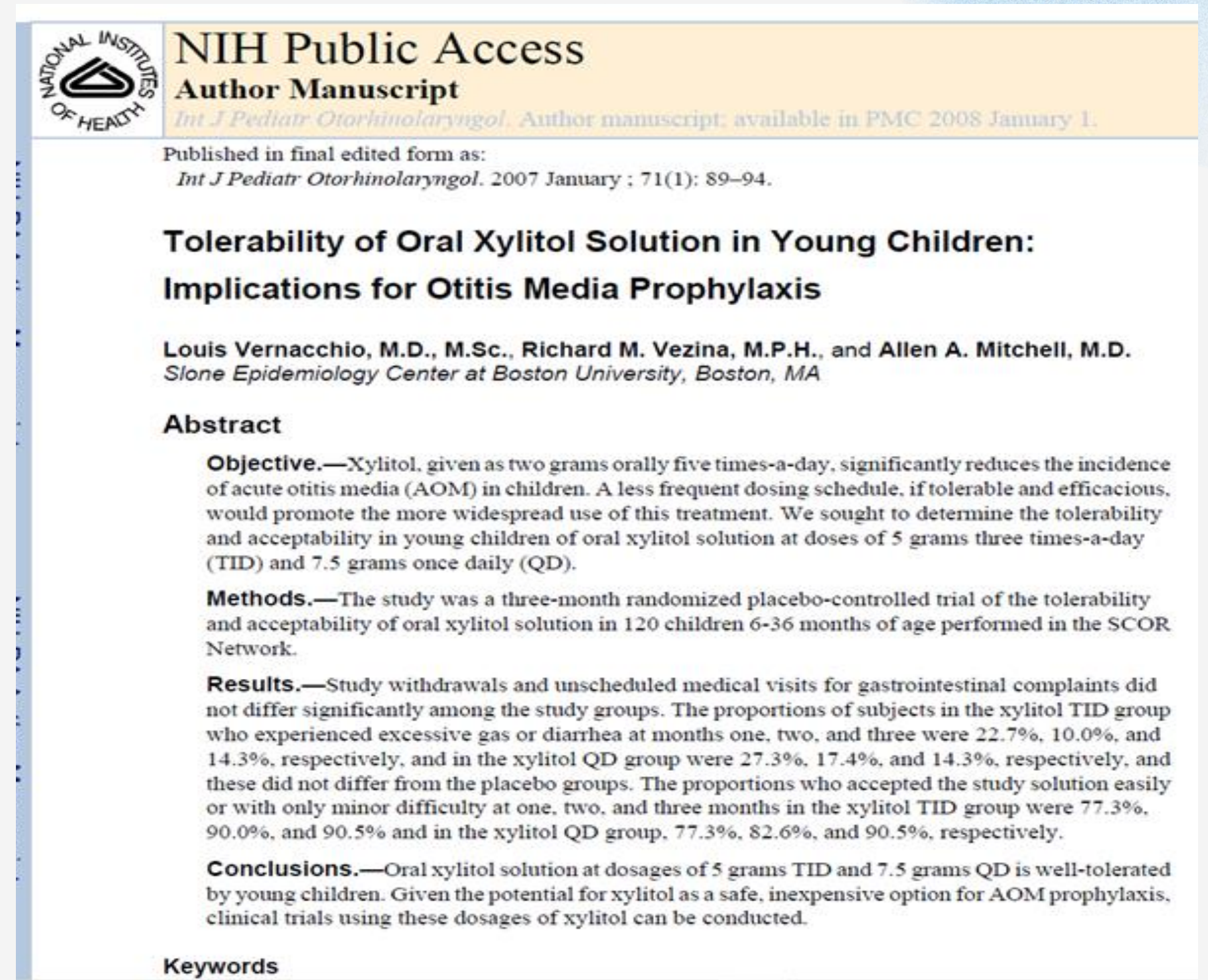




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Safety Profile of Xylitol

- Human studies: proven safe even in infants > 6 months of age
- No central-nervous-system or cardiovascular effects
- Non-irritating to nasal epithelium and enhances ciliary activity
- Demonstrates long-lasting nasal decongestion without rebound congestion.

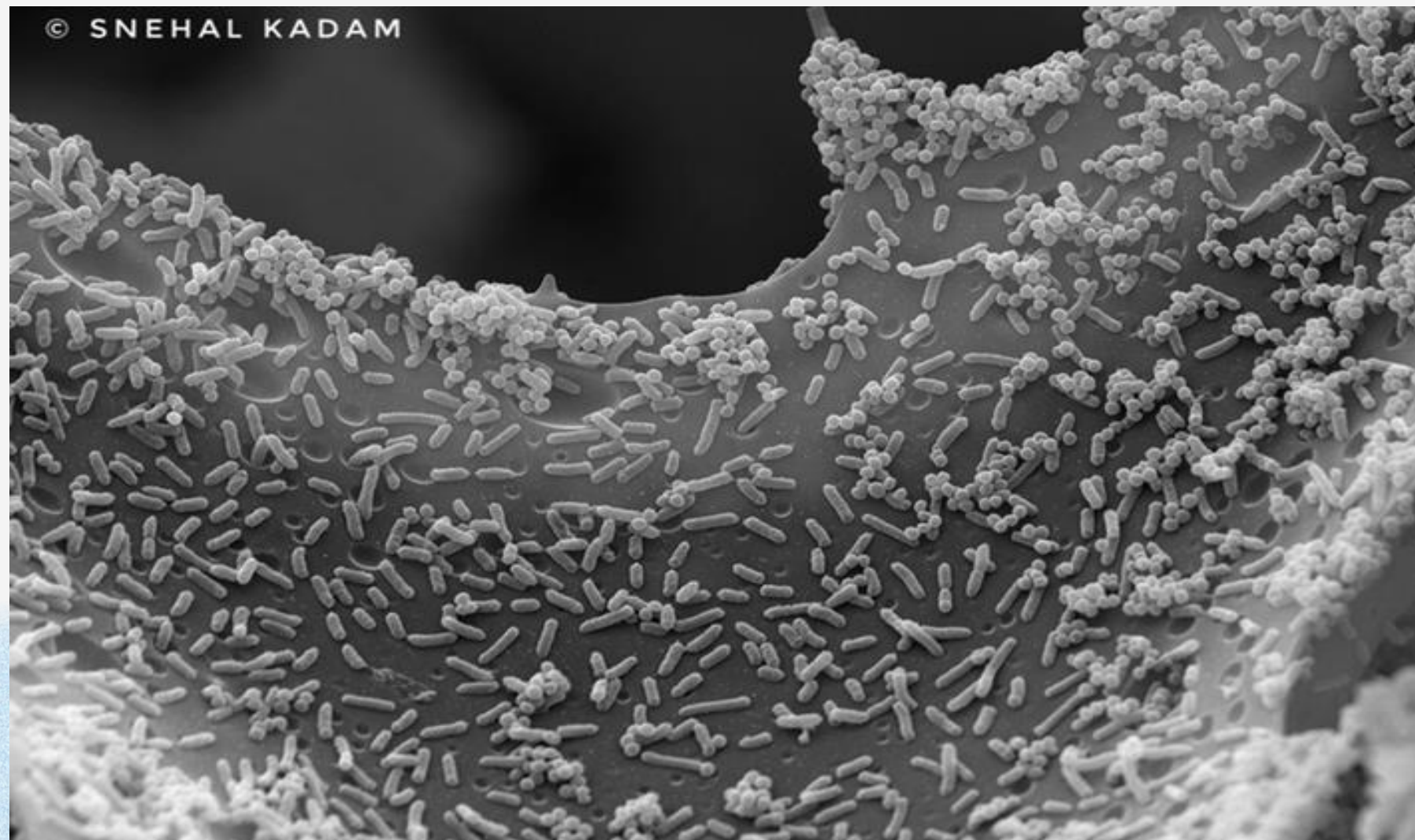


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Mechanism of Action of Xylitol in OCHI

Antibacterial & Anti-Biofilm:





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Evidence of Anti-Biofilm Activity

- Australian Journal of Otolaryngology (AJO, 2022) reported that xylitol inhibits biofilm growth of *S. aureus* and *H. influenzae*
- Demonstrated improved mucociliary clearance and reduced SNOT-22 symptom scores versus saline solution
- Reference: [AJO Study 2022](#)

Article

Efficacy and Safety of Xylitol Nasal Irrigation after Functional Endoscopic Sinus Surgery: A Randomized Controlled Study

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Abstract: Xylitol is considered a naturally occurring antibacterial agent. It is generally believed to enhance the body's own innate bactericidal mechanisms. It also provides anti-adhesive effects against both *Streptococcus pneumoniae* and *Haemophilus influenzae*. This study was performed to evaluate the efficacy and safety of xylitol nasal irrigation in the postoperative care of functional endoscopic sinus surgery (FESS). Patients with chronic rhinosinusitis who received FESS were recruited and randomly assigned to two groups at one month post-surgery. Thirty-five patients in the xylitol group received 400 mL of 5% xylitol nasal irrigation daily for 2 months, while another 35 in the normal saline (NS) group received 400 mL of NS nasal irrigation daily for 2 months. Prior to FESS, as well as before and after nasal irrigation, sinonasal symptoms were assessed through the 22-item Sino-Nasal Outcome Test Questionnaire. The patients also underwent an endoscopic examination while undergoing nasal function tests, and a cytokine measurement of the nasal lavage and a bacterial culture from the middle meatus were performed. The safety of the nasal irrigation was assessed through any self-reported adverse events, the Eustachian Tube Dysfunction Patient Questionnaire and the eustachian tube function test. The endoscopic scores and olfactory threshold significantly decreased after xylitol irrigation when compared with those before irrigation. The prevalence of *Staphylococcus aureus* in the nasal secretions also decreased significantly after xylitol irrigation. The amounts of Interleukin-5 and Interleukin-17A were significantly increased in the nasal lavage after xylitol irrigation. No side effects, including those related to eustachian tube function, were seen after nasal irrigation in both groups. Our results showed that xylitol nasal irrigation was both beneficial and safe during the postoperative care of FESS.

Keywords: chronic rhinosinusitis; functional endoscopic sinus surgery; nasal irrigation; normal saline; xylitol



Citation: Jiang, R.-S.; Chiang, Y.-F.; Liang, K.-L. Efficacy and Safety of Xylitol Nasal Irrigation after Functional Endoscopic Sinus Surgery: A Randomized Controlled Study. *Biomedicines* **2024**, *12*, 1377. <https://doi.org/10.3390/biomedicines12061377>

Academic Editors: Giuseppe Guida and Cristiano Caruso

Received: 19 May 2024

Revised: 14 June 2024

Accepted: 19 June 2024



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Antibacterial Mechanisms of Xylitol

- **Anti-Adhesion Effect**

Xylitol molecules, through their multiple hydroxyl (–OH) groups, bind to **glycoprotein receptors** on the nasal epithelial surface, **occupying the binding sites normally used by bacteria.**

As a result, Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus are **unable to adhere or colonize** the epithelium.

Outcome: Inhibition of the initial stage of infection (colonization inhibition)

- **Disruption of Bacterial Metabolism And movement**

Certain bacteria mistakenly take up xylitol via their glycolytic pathway but **cannot metabolize it completely.**

This leads to accumulation of toxic intermediates within bacterial cells, **impairing growth and cell division.**

Slowing down bacteria and **targeting them for macrophages**

Ref: Ruuskanen et al., Pediatrics 1998; 102(4): 879–884.



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Biofilms are microbial aggregates embedded in an extracellular polymeric matrix (EPS) with high resistance to treatment

Xylitol acts at two levels:

1.Pre-biofilm stage (Anti-adhesive):

Prevents initial bacterial adhesion to surfaces.

2.Mature biofilm stage:

Inhibits **EPS** polysaccharide synthesis, leading to structural collapse of the biofilm.

Proven in vitro and in vivo (AJO 2022) against *S. aureus* and *H. influenzae*.

Clinical evidence: chronic rhinosinusitis (CRS) patients using xylitol nasal irrigation showed significant improvement in SNOT-22 scores

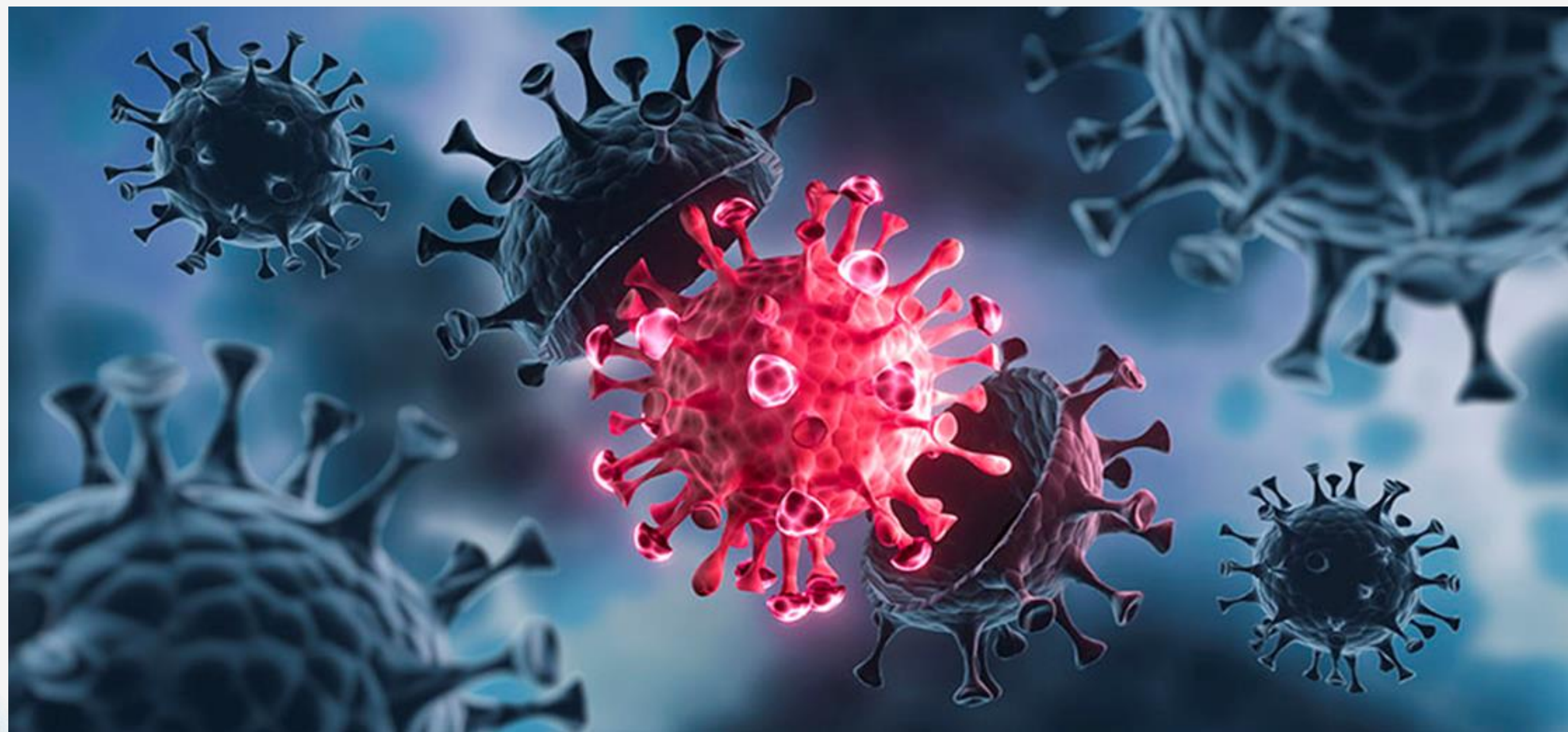
- **Molecular mechanism:**
- **Disrupts β -1,6-NACGLC (N-acetylglucosamine) linkages and downregulates biofilm-related genes (icaA, luxS).**

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Mechanism of Action of Xylitol in OCHI

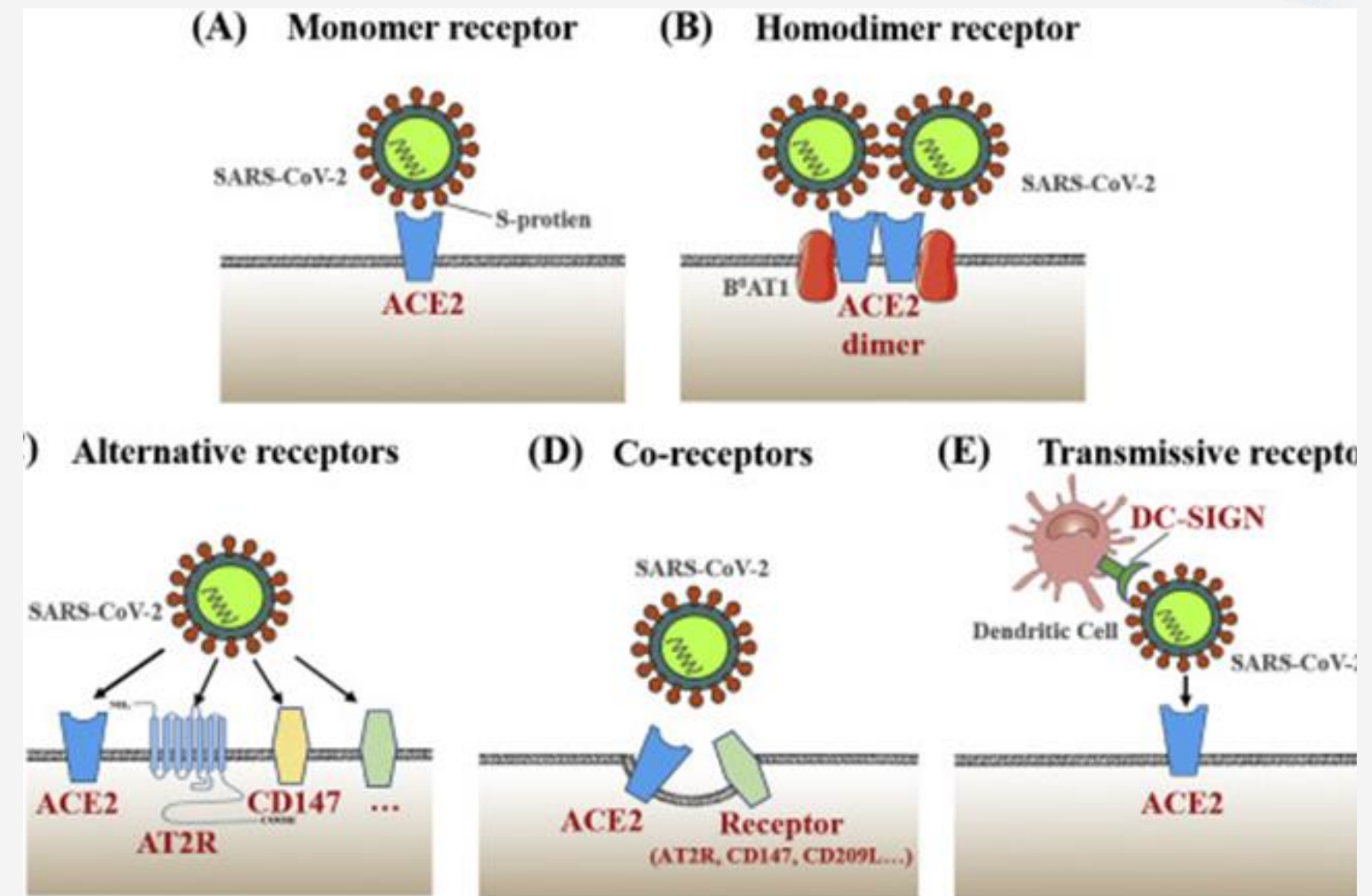
Antiviral:



Antiviral Mechanisms of Xylitol

Mechanism 1: Physical Inhibition of Viral Entry

- Xylitol forms a **moist glyco-mimetic layer** on the epithelial surface that **competitively blocks viral binding to glycosaminoglycan (GAG) receptors** such as sialic acid and heparan sulfate.
- In the case of SARS-CoV-2, this protective coating reduces viral entry through the ACE2 receptor pathway.
(Type I transmembrane glycoprotein)
- Studies (ESMED 2022; PMC9395150) reported up to a 45% reduction in viral entry.



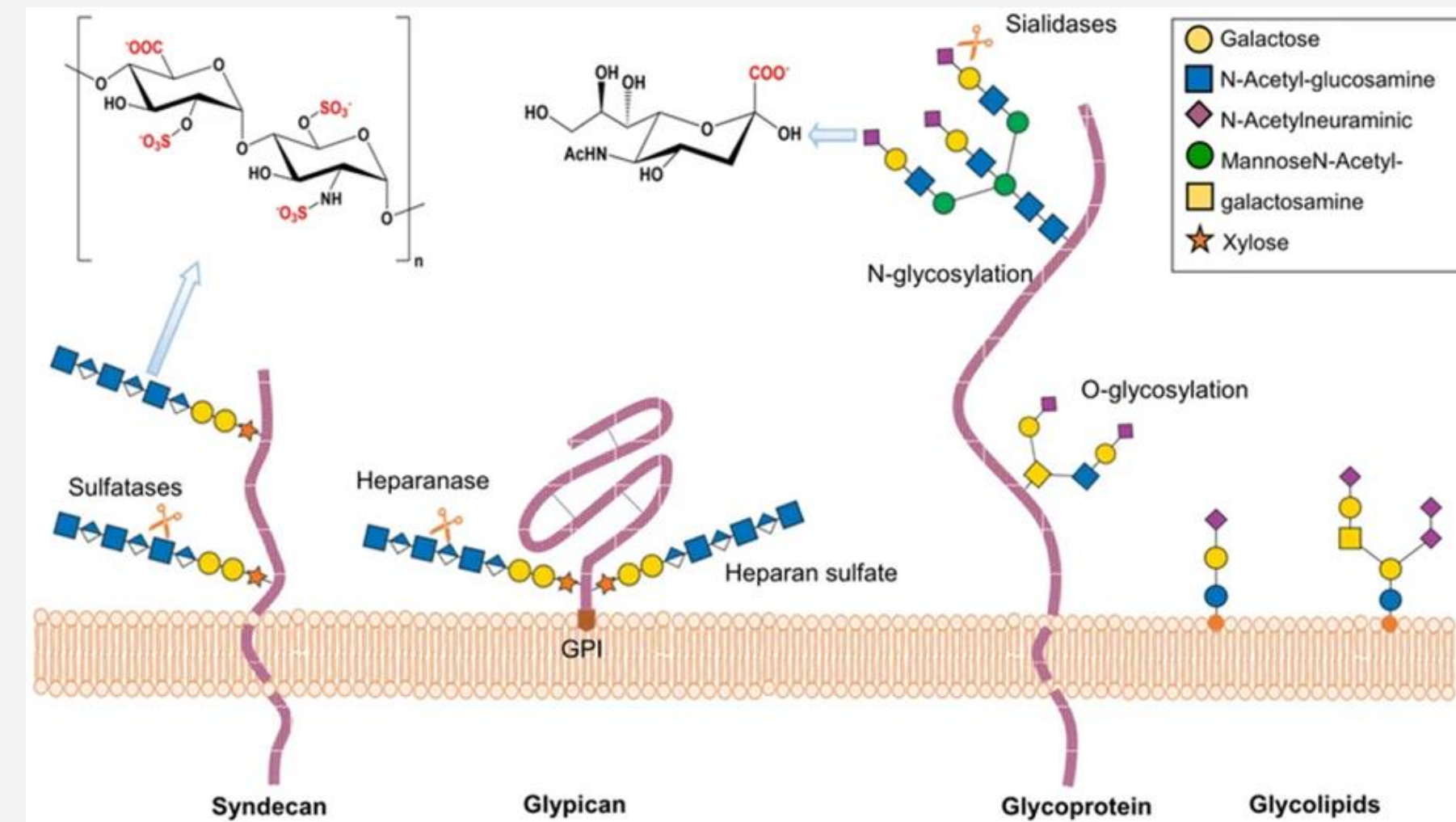


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Antiviral Mechanisms of Xylitol

Mechanism 2: Indirect Suppression of Viral Replication

- By **reducing opportunistic bacterial colonization and mucosal inflammation**, xylitol creates a less favorable environment for viral replication.
- Levels of **pro-inflammatory mediators (IL-6, MCP-1)** decrease, thereby limiting viral proliferation.





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Anti-Inflammatory, Osmolyte & Decongestant Effects of Xylitol

Anti-Inflammatory Activity:

In vitro studies show inhibition of **IL-6, IL-1 β , TNF- α** , and suppression of **NF- κ B activation**.
Leads to **reduction of local edema, redness, and nasal obstruction**.

Low-Tonicity (Osmolyte) Effect:

Xylitol is a **hypo-osmolar molecule** that reduces salt concentration in the epithelial lining fluid.

This **enhances innate antibacterial proteins** (lysozyme, defensins) and strengthens **local mucosal immunity**

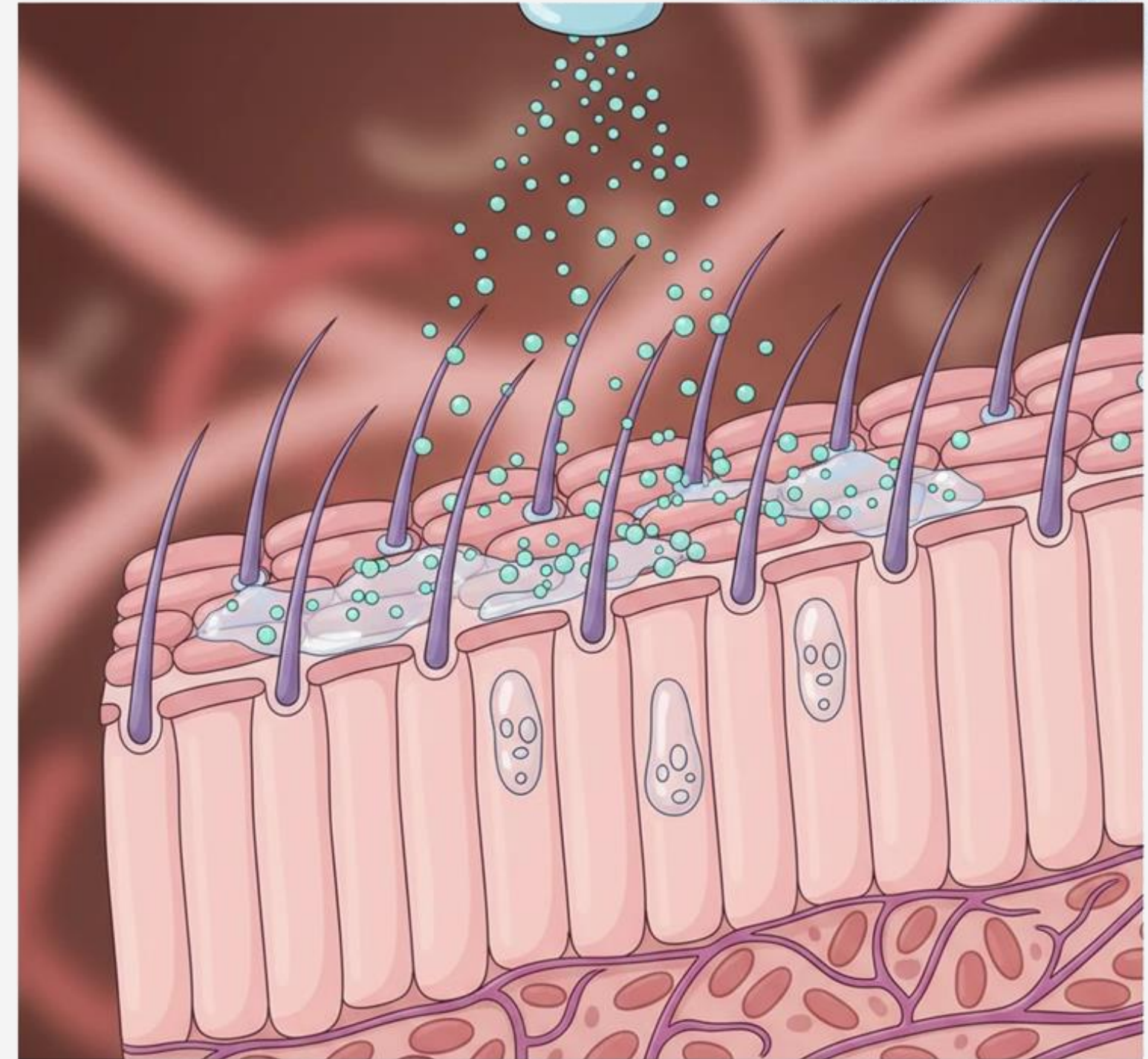
(Ref: PMC521689; PubMed 21994147).

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Mechanism of Action of Xylitol in OCHI

Anti-Inflammatory & Osmolyte Action:



Xylitol Nasal Spray: Epithelial Protection



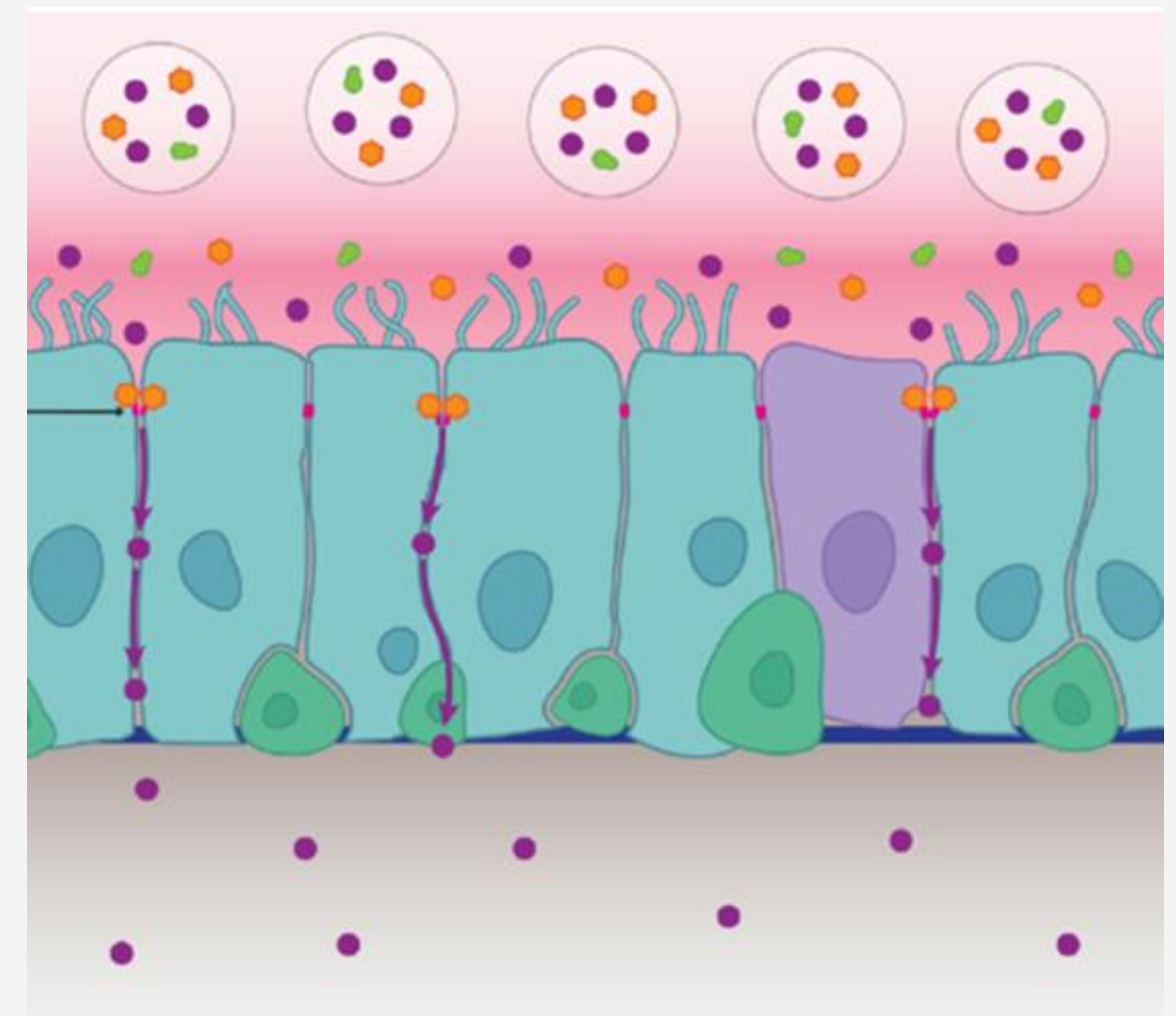
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Mild Hypo-Osmolar Action of Xylitol: Upward Water Movement for Sustained Mucosal Hydration

Three-Layer Structure of the Nasal Environment

Within the nasal epithelium, from outer to inner layers, we have:

- 1. Xylitol layer on the mucosal surface** – a mildly hypo-osmolar and hydrated solution.
- 2. Mucus layer (mucus + airway surface liquid)** – usually slightly more concentrated.
- 3. Submucosal (interstitial) fluid layer** – with osmolarity close to plasma (~300 mOsm).

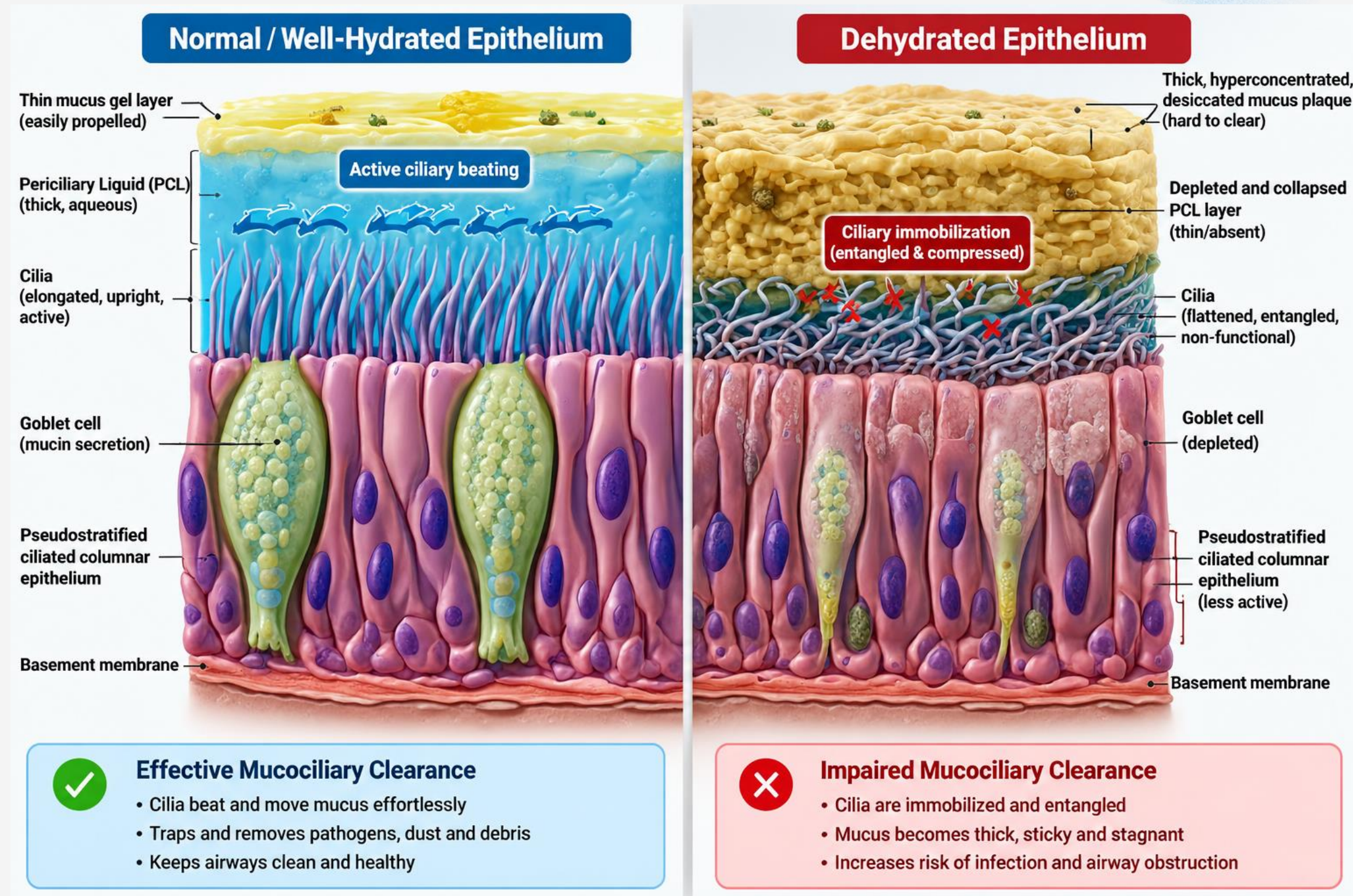


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Improved Ciliary Function:

By restoring epithelial hydration and lowering osmotic stress, xylitol enhances ciliary beating, promoting mucociliary clearance and reducing nasal congestion.





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Clinical Indications for OCHI

- Acute and chronic rhinosinusitis
- Allergic and non-allergic rhinitis
- Prevention of recurrent upper-respiratory infections (URIs) in preschool children
- **Post-nasal or sinus surgery care** (e.g., FESS, septoplasty)
- Supportive combination with **antibiotic** or **phytotherapeutic** treatments (e.g., Pelargonium)



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Dosage and Use (Pediatric Focus)

- Practical, pediatric-friendly spray formulation
- Typically 1–2 sprays per nostril, 2–3 times daily
- Can be used continuously for hygiene and prevention without dependency



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Pharmacology of Xylitol

- **Pharmacokinetics (PK):**
 - Negligible systemic absorption ($\leq 2\%$)
 - Predominantly remains on the nasal epithelium and mucosal surface
 - Partial metabolism through pentose-phosphate pathway to glucose
 - Eliminated renally in unchanged form
- **Pharmacodynamics (PD):**
 - Rapid onset of action (within minutes)
 - Local effect lasting 4–6 hours
 - No drug interactions or systemic involvement
 - Safe for repeated use in young children and special patient populations



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Metabolic Nature & Absorption Profile of Xylitol

Chemical Nature:

- Xylitol is a natural pentitol ($C_5H_{12}O_5$) that undergoes endogenous metabolism via the Pentose Phosphate Pathway (PPP).

Metabolic Conversion:

- It is enzymatically converted to D-Xylulose-5-Phosphate by xylitol dehydrogenase and xylulokinase, integrating into normal energy-producing cellular routes.

Pharmacological Classification:

- Since it enters physiologic metabolic pathways and has no specific receptor or drug target, xylitol is not a drug, but a bio-compatible polyol metabolite.

Systemic Absorption:

- Intranasal xylitol (as in OCHI Nasal Spray) shows negligible systemic uptake (< 2%) — meaning it does not reach systemic circulation in biologically significant amounts and produces no systemic pharmacologic effect.



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Comparison with Saline (NaCl)

Parameter	Isotonic Saline	Xylitol (OCHI)
Hydration	Moderate	High and long-lasting
Anti-biofilm	None	Present
Anti-inflammatory	Limited	Significant
Comfort	May cause dryness	Sustained moisture
Congestion relief	Short-term	Durable
Pediatric safety	High	Very high (multiple studies)



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Summary of Efficacy and Advantages

- Potent **antibacterial** effect on nasal mucosa
- **Antiviral and anti-inflammatory** benefits without epithelial damage
- Natural **humectant & osmolyte**
- **Sustained decongestion** with zero rebound
- **Safe, non-addictive, systemically inert**



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Essential References for Final Slide

1. Ruuskanen O. et al., Pediatrics 1998; 102(4): 879–884
2. AJO 2022 – Xylitol in Sinonasal Disease
3. ScienceDirect 2023 – Effectiveness of Xylitol Spray in Children
4. PMC17249 – Xylitol and Airway Infections
5. ESMED 2022 – Antiviral Potential of Sugar Alcohols
6. PubMed 21994147 – Chronic Rhinosinusitis Irrigation Study

FOLIMAX®

HELIOS





Folimax is a drop of folic acid made by the ALLTONE UK company, which has the following benefits:

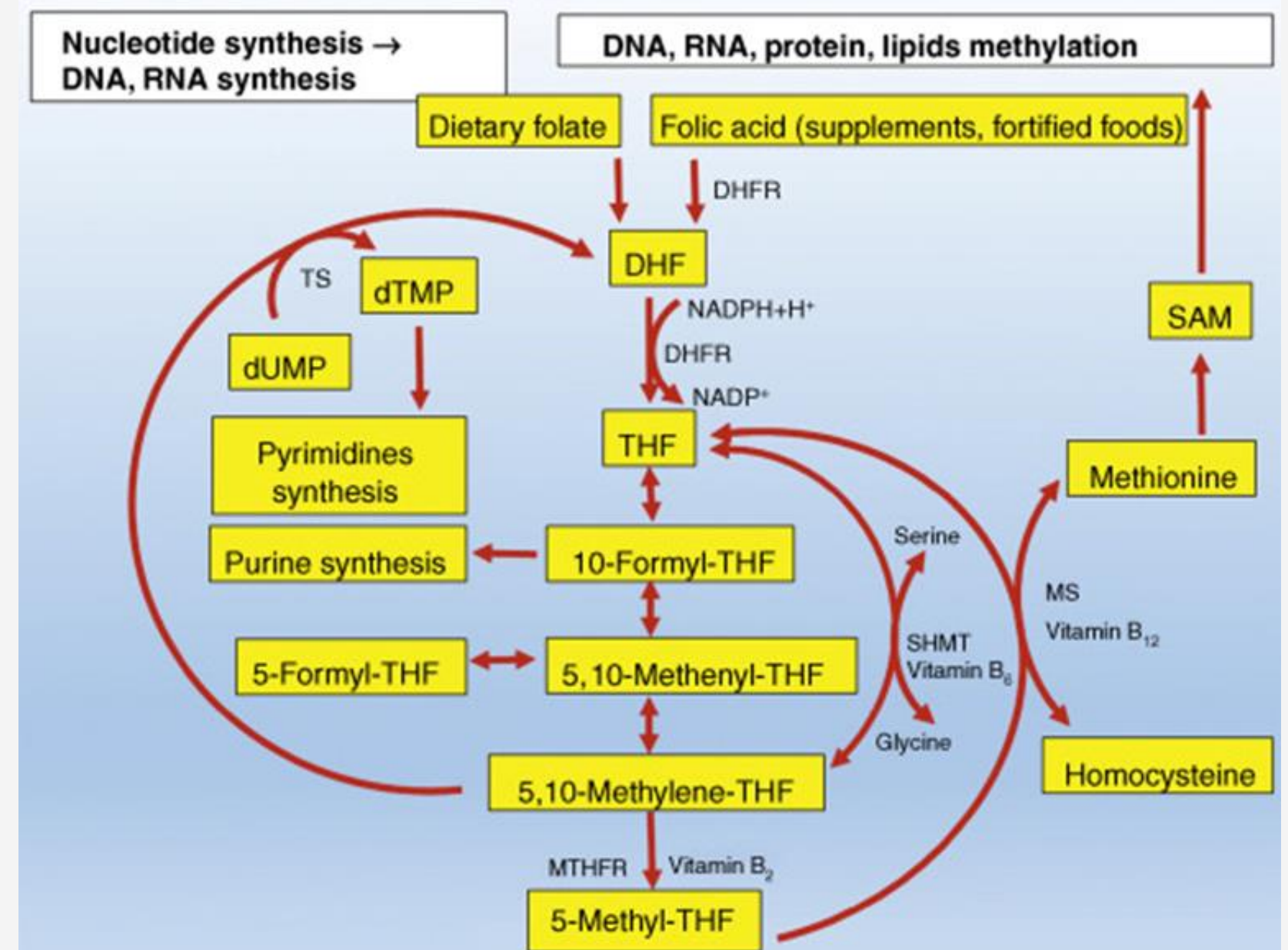
- The first drop of folic acid in Iran
- Contains 400 micrograms per ml
- Free of parabens, alcohol, gluten, artificial colors and eggs
- Excellent taste





folic acid metabolism pathway

After intestinal absorption, folic acid is first converted to DHF and then to THF by **the enzyme Dihydrofolate** reductase (DHFR) in the intestines and liver, and finally enters the methylation cycle and essential pathways of cell proliferation, DNA formation, and neuronal function





Orphanet – Dihydrofolate reductase deficiency (updated 2024) NIH – Genetic and Rare Diseases Information Center (GARD)

DHFR deficiency is an extremely rare metabolic disorder, with a prevalence of less than 1 in 1,000,000 individuals worldwide.

What is the Genetic and Rare Diseases Information Center?

Progress in data science and an increased understanding of disease genetics lead experts to agree that more than an estimated 10,000 rare diseases affect millions of people in the United States. Each disease may be rare individually, but people with rare diseases often face similar challenges. These challenges may include accessing information, getting a diagnosis, and finding resources.

The mission of the Genetic and Rare Diseases (GARD) Information Center is to help the rare disease community meet these common challenges. We do this by providing free access to reliable and easy-to-

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Knowledge on rare diseases and orphan drugs

"Rare diseases are rare, but rare disease patients are numerous"

Access our Services

Inventory, classification and encyclopaedia of rare diseases, with genes involved

Inventory of orphan drugs

Directory of patient organisations

Directory of professionals and institutions



Dihydrofolate reductase (DHFR) deficiency is a rare autosomal recessive disorder of folate metabolism



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RESEARCH ARTICLE · Volume 583, P84-92, September 13, 2025

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Identification of novel disease-causing variants and their influence on clinical presentation in dihydrofolate reductase deficiency

Dandan Wang · Dengyu Zhou · Yuanyuan Zhang · Weiwei Lu · Zhihua Luo

Affiliations & NotesArticle Info

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Highlights

- First Chinese *DHFR* deficiency pedigree expands global variant spectrum.
- Novel p.Leu22Pro/p.Arg135His variants reduce DHFR protein expression.
- Variants impair the substrate binding capacity of DHFR protein.
- Folinic acid alleviates neurological symptoms of *DHFR* deficiency.
- Multilevel functional validation aids rare disease diagnosis.

Graphical abstract

Figures (4)

Figure Viewer

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Abstract

Dihydrofolate reductase (DHFR) deficiency is a rare autosomal recessive disorder of folate metabolism, which is crucial for DNA/RNA synthesis and normal growth. Only seven molecularly confirmed cases, all presenting with megaloblastic anemia and neurological symptoms, have been reported. We report two cases from a non-consanguineous Chinese family. The proband presented with neonatal seizures; folic acid improved neurological symptoms but did not prevent fatal respiratory failure. His sister had severe megaloblastic anemia. Whole-exome sequencing identified two compound heterozygous variants in *DHFR* (p.Gly18Val and p.Pro26Leu) in both patients. Structural modeling suggested these variants to compromise protein stability/function. Variant protein expression plasmids produced significantly less DHFR protein than wild-type plasmid as indicated by western blot and ELISA analyses. Methotrexate fluorescence binding assays indicated reduced binding capacity, suggesting potential structural alterations in the variant proteins. These results demonstrate that the variants lead to decreased DHFR protein abundance and perhaps altered molecular interactions, supporting their pathogenicity. Our findings underscore the critical importance of early genetic testing for patients with megaloblastic anemia or neurological symptoms to diagnose *DHFR* deficiency. Early detection and treatment are essential to improve prognosis and prevent severe outcomes.

Keywords

DHFR · Dihydrofolate reductase deficiency · Megaloblastic anemia · Epilepsy

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Supplementary materials (2)

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Document (17.61 KB)Supplementary Data 1

Document (1.57 MB)Supplementary Data 2

Related articles (40)



Superior Absorption and Efficacy of Folic Acid Compared to Natural Folate

Clinically and biochemically, synthetic **folic acid** (the form in Folicacid) shows **20–70% higher bioavailability** than dietary folates, achieving optimal blood folate levels with **lower doses** and representing the **more effective, stable, and clinically standardized** form.

Bioavailability of food folates is 80% of that of folic acid^{1–3}

Renate M Winkels, Ingeborg A Brouwer, Els Siebelink, Martijn B Katan, and Petra Verhoef

ABSTRACT

Background: The bioavailability of natural food folates is lower than that of synthetic folic acid, but no agreement exists as to the extent of the difference.

Objective: In a 4-wk dietary intervention study, we determined the aggregate bioavailability of food folates from fruit, vegetables, and liver relative to that of folic acid.

Design: Seventy-two healthy adults were randomly divided into 4 treatment groups. Group A ($n = 29$) received a high-folate diet with 369 μg food folate/d and a placebo capsule; groups B, C, and D ($n = 14$ or 15) received a low-folate diet with 73 μg food folate/d and folic acid capsules. These capsules contained 92 μg folic acid/d for group B, 191 μg for group C, and 289 μg for group D. In addition, all 72 subjects daily ingested a capsule with 58 μg [$^{13}\text{C}_{11}$]-labeled folic acid. We measured the percentage of [$^{13}\text{C}_{11}$]-labeled folate in plasma folate at the end of the intervention and ascertained the changes in serum folate concentrations over the 4 wk of the intervention.

Results: Bioavailability of food folate relative to that of folic acid was 78% (95% CI: 48%, 108%) according to [$^{13}\text{C}_{11}$]-labeled folate and 85% (52%, 118%) according to changes in serum folate concentrations.

Conclusions: The aggregate bioavailability of folates from fruit, vegetables, and liver is $\approx 80\%$ of that of folic acid. The consumption of a diet rich in food folate can improve the folate status of a population more efficiently than is generally assumed. *Am J Clin Nutr* 2007;85:465–73.

KEY WORDS Food folate, bioavailability, folic acid, stable isotopes

Folate bioavailability is defined as the proportion of an ingested amount of folate that is absorbed in the gut and that becomes available for metabolic processes. In human intervention studies, relative bioavailability is usually assessed by comparison with a reference dose of folic acid. The bioavailability of food folate is generally lower than that of folic acid, but the extent of the difference is unclear (11, 12).

Recommended daily allowances for food folate take into account its lower bioavailability. The basis for adapting the US recommendations for folate to the lower bioavailability of food folate (5) was derived from a study by Sauberlich et al (13), which stated that the bioavailability of food folate was no more than 50% of that of folic acid. Unfortunately, they did not indicate how that finding was obtained.

Other long-term dietary intervention studies found bioavailability estimates between 30% and 98% of those of folic acid (14, 15). Thus, no clear figure exists for the bioavailability of natural folates as a proportion of that of folic acid. We therefore performed a large, long-term dietary intervention study in which we compared the bioavailability of food folate with that of different doses of folic acid; we simultaneously assessed bioavailability from changes in serum folate concentrations and from stable isotope dilution.

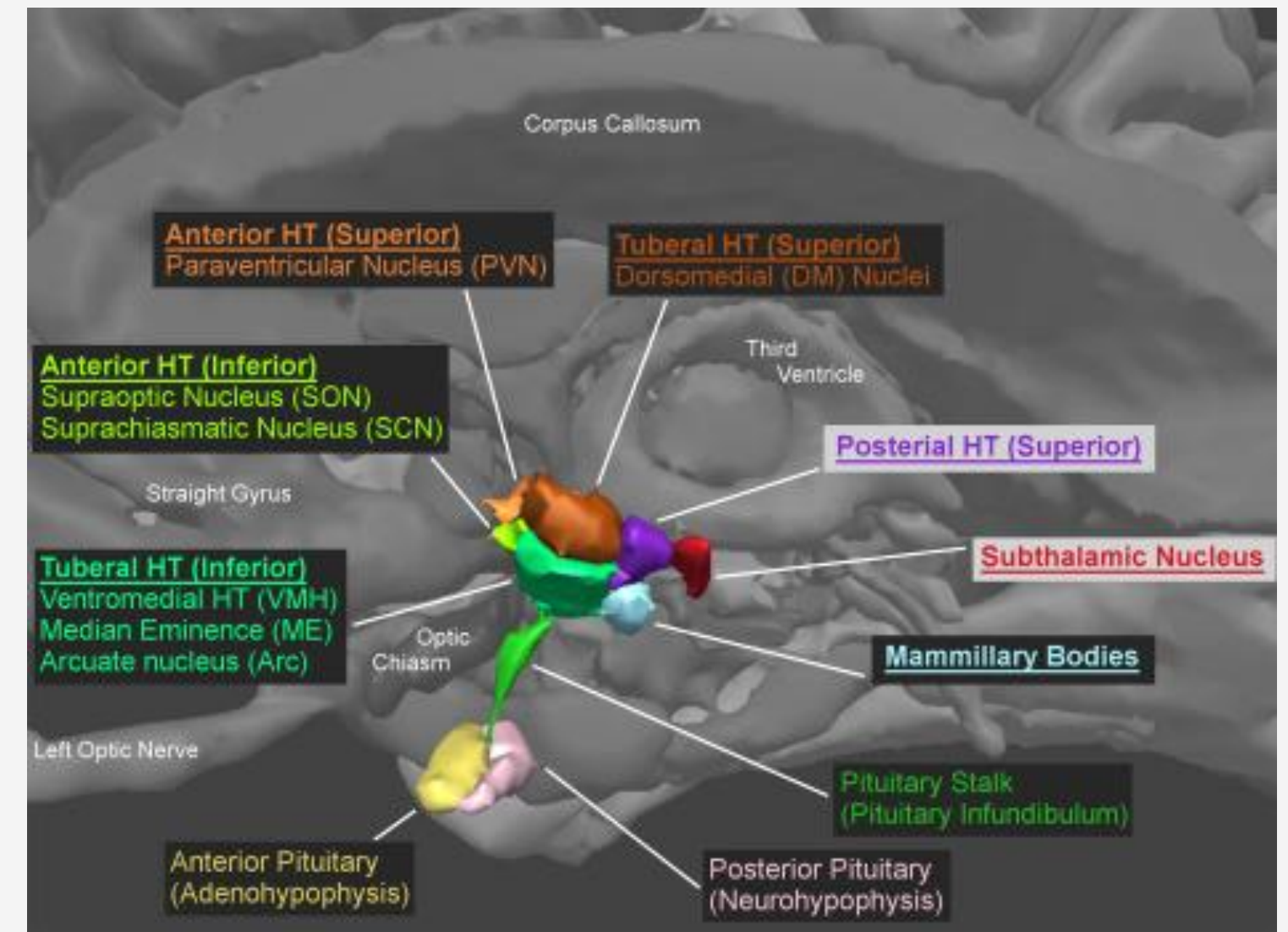
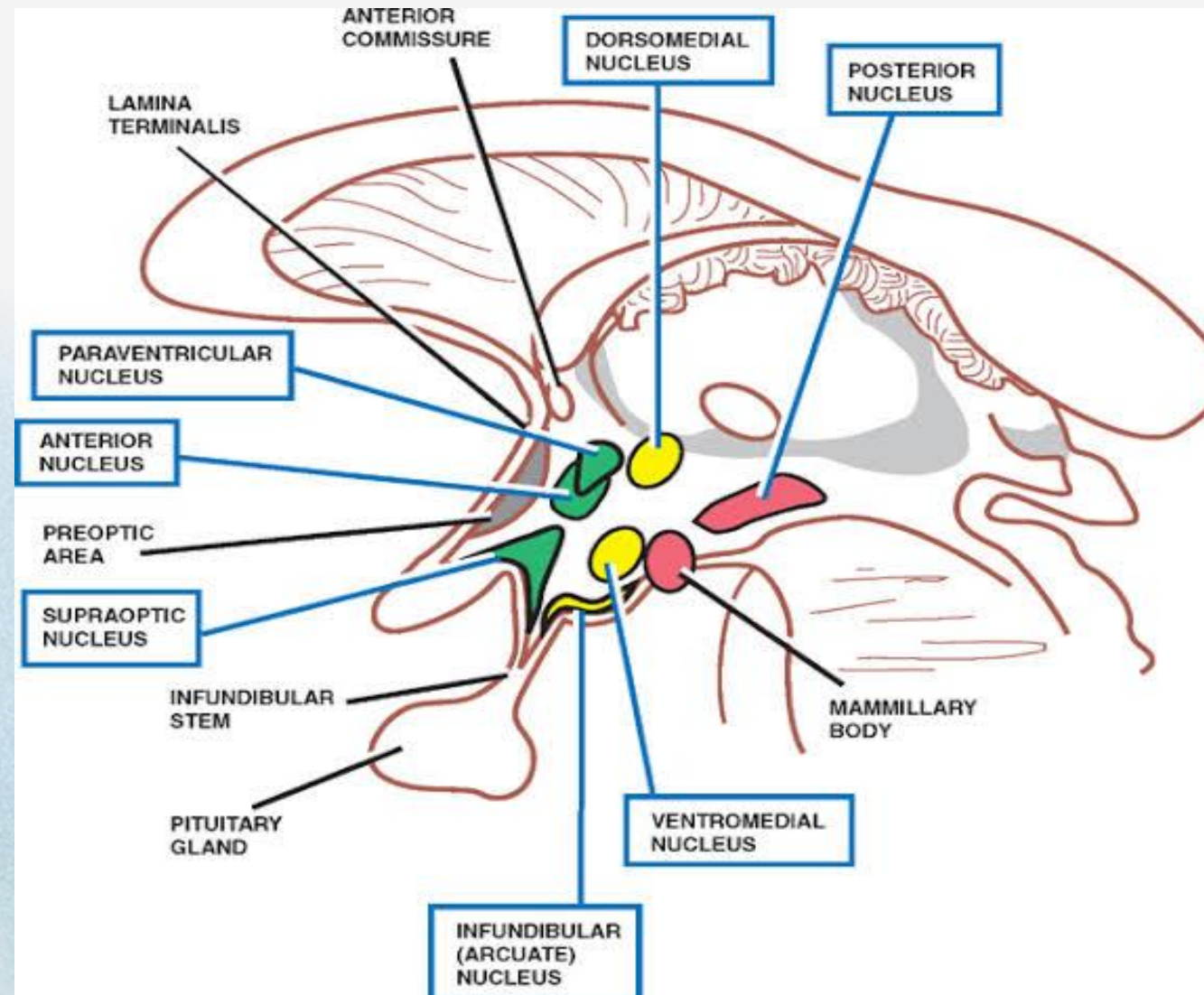
SUBJECTS AND METHODS

Subjects

Ninety-three healthy men and women, recruited from among the staff and students of Wageningen University and the population of the city of Wageningen, volunteered to take part in the

Indication:

- best for preterm
 - neural tube defects (NTD)
 - macrocytosis and megaloblastic anemia
 - Restoring the intestinal villi and epithelial tissue of the digestive system during digestive infections and long-term use of antibiotics
 - Increase children's appetite(fetal and neonatal)
-
- Development of dopaminergic neurons and the cell bodies of neurons in the ventromedial hypothalamic nucleus





Int J Mol Sci 2019 Oct 14;20(20):5097. doi: 10.3390/ijms20205097.

Methyl Donor Deficiency during Gestation and Lactation in the Rat Affects the Expression of Neuropeptides and Related Receptors in the Hypothalamus

Lynda Saber Cherif 1, Grégory Pourié 2, Andréa Geoffroy 3, Amélia Julien 4, Déborah Helle, Aurélie Robert 5, Rémy Umoret, Jean-Louis Guéant 6, Carine Bossenmeyer-Pourié 7, Jean-Luc Daval 8

Affiliations Expand

PMID: 31615150 PMCID: PMC6829491 DOI: 10.3390/ijms20205097

Abstract

The micronutrient vitamin B9 act as methyl donors in the one-carbon metabolism involved in transmethylation reactions which critically influence epigenetic mechanisms and gene expression. B9 vitamin is essential for proper development, and their deficiency during pregnancy has been associated with a wide range of disorders, including persisting growth retardation. Energy homeostasis and feeding are centrally regulated by the hypothalamus which integrates peripheral signals and acts through several orexigenic and anorexigenic mediators. We studied this regulating system in a rat model of methyl donor deficiency during gestation and lactation. At weaning, a predominance of the anorexigenic pathway was observed in deficient pups, with increased plasma peptide YY and increased hypothalamic pro-opiomelanocortin (POMC) mRNA, in line with abnormal leptin, ghrelin, and insulin secretion and/or signaling during critical periods of fetal and/or postnatal development of the hypothalamus. These results suggest that early methyl donor deficiency can affect the development and function of energy balance circuits, resulting in growth and weight deficits. Maternal administration of folic acid (3 mg/kg/day) during the perinatal period tended to rectify peripheral metabolic signaling and central neuropeptide and receptor expression, leading to reduced growth retardation.



Original Article

Effects of folic acid on preschool children's appetite: Randomized triple-blind clinical trial

NIKTA HATAMIZADEH,^{1,2} HASSAN EFTEKHAR,³ BIJAN SHAFAGHI⁴ AND KAZEM MOHAMMAD⁵

Departments of ¹Clinical Medicine and ²Rehabilitation Management, University of Social Welfare and Rehabilitation Sciences, Departments of ³Family Health and ⁵Biostatistics, School of Public Health, Tehran University of Medical Sciences, and ⁴Department of Toxicology, Faculty of Pharmacology, Shaheed Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: In recent years some Iranian pediatricians have used folic acid empirically as an appetite-enhancing drug in poor-appetite, low-weight children. Many parents have expressed their satisfaction with this treatment but until now no study has been done to confirm or exclude folic acid as an appetite enhancer.

Methods: In order to determine if complementary folic acid has any effect on preschool children's appetite, 61 3–5-year-old children (27 girls and 34 boys) whose weight/age and weight/height ratios were below the 25 centile and whose parents regarded them as having poor appetite were randomly assigned to receive either folic acid (1 mg/day) or placebo for 20 days. The primary outcome measures were any appetite changes during and 1 month after the end of the intervention, measured by means of a questionnaire completed by parents on the 20th and 60th days. Secondary measures were mean weight gain on the 30th and 60th days.

Results: Children who received folic supplement had a significantly better appetite on the 20th day than those who received placebo (mean difference of appetite score: 1.7; 95% confidence interval: 0.1–3.4; $P=0.04$) and significantly more children receiving folic acid were reported to have increased appetite than the placebo group ($P=0.03$). But 40 days after the end of the intervention there was no difference between the two groups. Weight gain did not significantly differ between groups.

Conclusions: Although folic acid appears to improve preschool children's appetite, further study is necessary to determine whether it has any effect on growth as an adjunctive to management protocols of low appetite for undernourished children.



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Nutrition

Volume 30, Issue 3, March 2014, Pages 274-278



Applied nutritional investigation

Effect of folic acid on appetite in children: Ordinal logistic and fuzzy logistic regressions

Mahshid Namdari Ph.D. (candidate)^a, Alireza Abadi Ph.D.^b  , S. Mahmoud Taheri Ph.D.^c,
Mansour Rezaei Ph.D.^d, Naser Kalantari M.D.^e, Nasrin Omidvar M.D.^e

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can lead to malnutrition, a leading cause of impaired growth and mortality in childhood. It is occasionally considered that folic acid has a positive effect on appetite enhancement and consequently growth in children. The aim of this study was to assess the effect of folic acid on the appetite of preschool children 3 to 6 y old.

Methods

The study sample included 127 children ages 3 to 6 who were randomly selected from 20 preschools in the city of Tehran in 2011. Since appetite was measured by linguistic terms, a fuzzy logistic regression was applied for modeling. The obtained results were compared with a statistical ordinal logistic model.

Results

After controlling for the potential confounders, in a statistical ordinal logistic model, serum folate showed a significantly positive effect on appetite. A small but positive effect of folate was detected by fuzzy logistic regression. Based on fuzzy regression, the risk for poor appetite in preschool children was related to the employment status of their mothers.

Conclusions

In this study, a positive association was detected between the levels of serum folate and improved appetite. For further investigation, a randomized controlled, double-blind clinical trial could be helpful to address causality.



Folate in gastrointestinal health and disease

F R Ponziani ¹, I A Cazzato, S Danese, S Faggioli, P Gionchetti, B E Annicchiarico, F D'Aversa, A Gasbarrini

Affiliations + expand

PMID: 22530356

Abstract

Objective: Folate has heterogeneous functions and is involved in several activities in both animal and human body. It is an important constituent of our organism, and its bioavailability is mainly dependent from the correct function of our gastrointestinal tract. Our aim is to describe what happens to folate homeostasis in gastrointestinal health and disease, analyzing the alterations of folate metabolism in some specific conditions of intestinal and liver impairment.

Discussion: Folate absorption and metabolization involve the small intestine and the liver; in conditions of gastrointestinal tract disease (i.e. celiac disease, liver disease) folate function may be compromised with important consequences on the whole organism. Moreover, folate deficiency may produce gastrointestinal alterations too. For this reason, the gastrointestinal tract could be the responsible but also the victim of folate deficiency.

Conclusions: The presence of folate deficiency should always be assessed in patients with a gastrointestinal disease. Further studies are needed to assess the role of folates in gastrointestinal tract diseases and in other gynecologic, neurologic, psychiatric, cardiovascular, ophthalmic and neoplastic diseases. Folate supplementation could be considered, in the future, as an effective complementary therapy in several pathologic conditions.



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Product Introduction

10-Minute Pediatric Conference Presentation

- Ready-to-Use Oral Rehydration Solution

OneLyte: Ready-to-Use Oral Electrolyte Solution

- First ready to use ORS meeting global osmolarity standards
- WHO-compliant formulation
- open and drink, no prep required
- Contains highly bioavailable Zinc Gluconate
- Three flavors: Green Apple, Pomegranate and Original



HELIOS

Product Introduction

Each liter contains 100 kcal

- Dextrose: 25 g/L
- Potassium: 20 mEq/L
- Sodium: 45 mEq/L
- Chloride: 35 mEq/L
- Zinc: 7.8 mg/L
- Osmolarity: 245 mOsm/L
- Bottle volume: 500 mL ($\pm 4\%$)





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OPEN

Potency of Oral Rehydration Solution in Inducing Fluid Absorption is Related to Glucose Concentration

Vittoria Buccigrossi, Andrea Lo Vecchio, Eugenia Bruzzese, Carla Russo, Antonella Marano, Sara Terranova, Valentina Cioffi & Alfredo Guarino 

Oral rehydration solutions (ORSs) is the key treatment of acute diarrhea in children, as it restores the electrolyte balance by stimulating the intestinal sodium/glucose transporter SGLT1 to induce fluid absorption. The World Health Organization (WHO) and The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) proposed ORSs with different chemical compositions. The main agent of childhood acute gastroenteritis is rotavirus (RV). We evaluate the effects of ORS with different concentration of glucose and sodium on RV induced secretion. Ussing chambers technique was used for electrophysiology experiments to evaluate ion fluid flux. ESPGHAN ORS (sodium 60 mmol/L and glucose 111 mmol/L) induced a more potent proabsorptive effect in Caco-2 cells than WHO ORS, and this effect depended on the sodium/glucose ratio. Titration experiments showed that RV-induced fluid secretion can be reverted to a proabsorptive direction when sodium and glucose concentration fall in specific ranges, specifically 45–60 mEq/L and 80–110 mM respectively. The results were confirmed by testing commercial ORSs. These findings indicated that ORS proabsorptive potency depends on sodium and glucose concentrations. Optimal ORS composition should be tailored to reduce RV-induced ion secretion by also considering palatability. These *in vitro* data should be confirmed by clinical trials.

In 1978, an editorial in the Lancet reported “The discovery that sodium transport and glucose transport are coupled in the small intestine so that glucose accelerates absorption of solute and water, is potentially the most important medical advance of this century¹”. Millions of lives of children and adults were saved by the use of a simple mixture of salt-glucose².

Diarrhea is already an important cause of death primarily in children younger than 5 years. Approximately 1.3 million deaths are caused by diarrheal diseases among all ages, with the main impact on children younger than 5 years^{3,4}. Fatal gastroenteritis occurs mainly in developing countries because of poor hygiene and malnutrition (300,000 deaths/year in sub-Saharan Africa), although fatality should not be neglected in the high-income countries (approximately 700 deaths/year in 2015)^{5,6}. Rotavirus is the most frequent diarrheal disease causing high mortality in children younger than 5 years (150,000 deaths in 2015) with also an significant rate in older ones (200,000 deaths among all ages)⁶. The severity of gastroenteritis corresponds to the degree of dehydration defined by the amount of water and electrolyte losses. Hence, the current management of diarrhea in children involves the prevention and management of dehydration as first line therapy.

Oral rehydration solution (ORS) is a balanced mixture of glucose and electrolytes that stimulates fluid absorption and counteracts dehydration and metabolic acidosis and is used for the rehydration. ORS efficacy exploits the Na⁺/glucose cotransporter (SGLT1), located on the apical membrane of intestinal epithelial cells⁷.

The first ORS composition was jointly proposed by the United Nations Children's Fund (UNICEF) and the

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Composition of oral rehydration solutions (ORS) and commonly used beverages

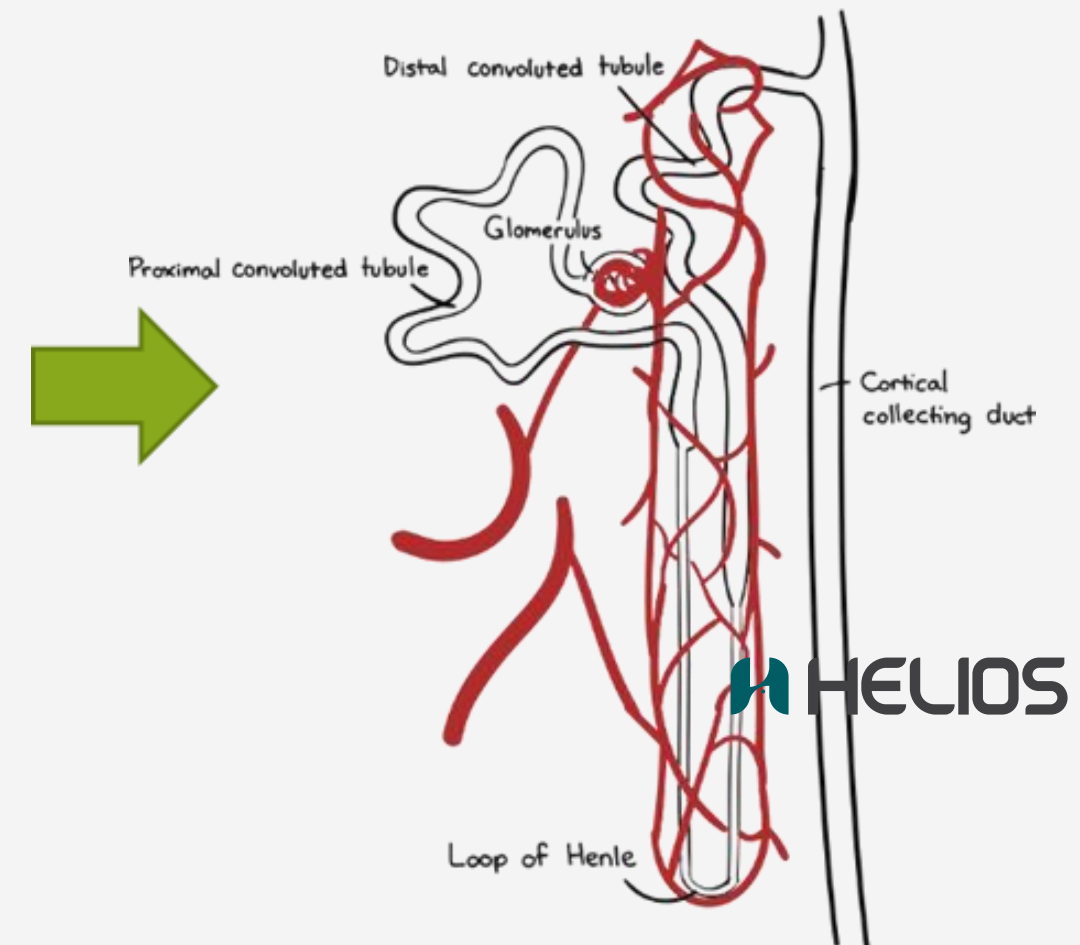
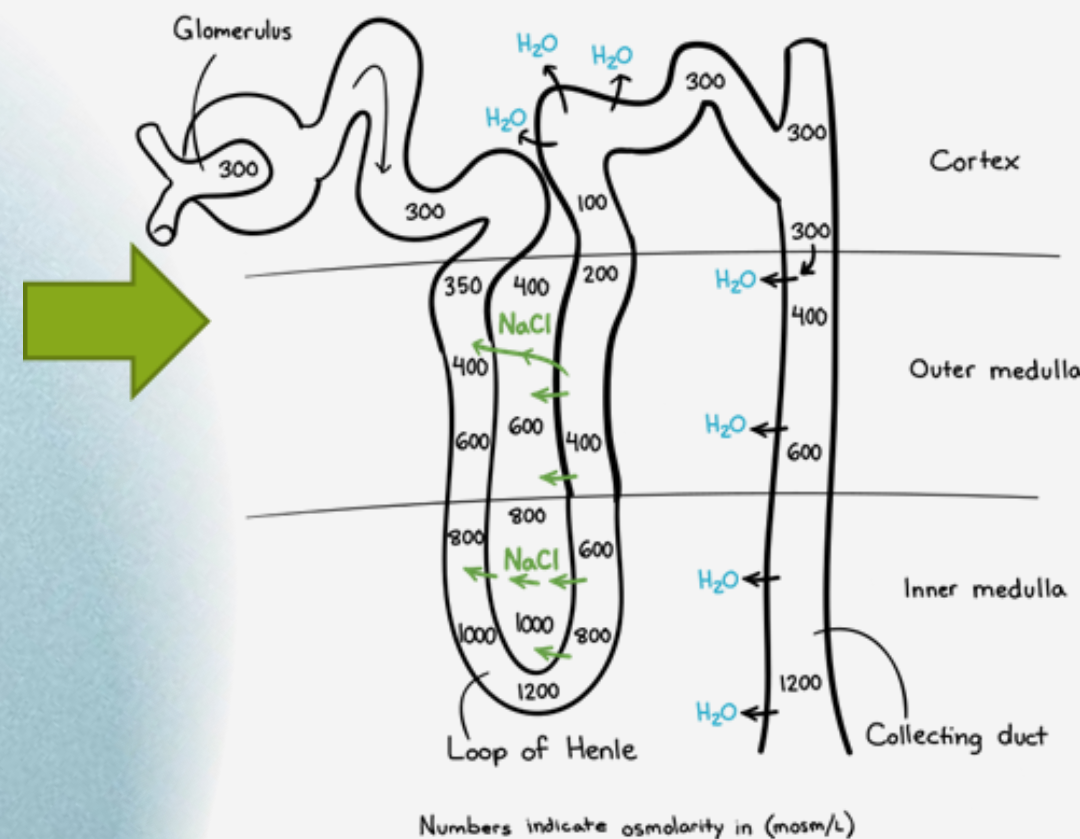
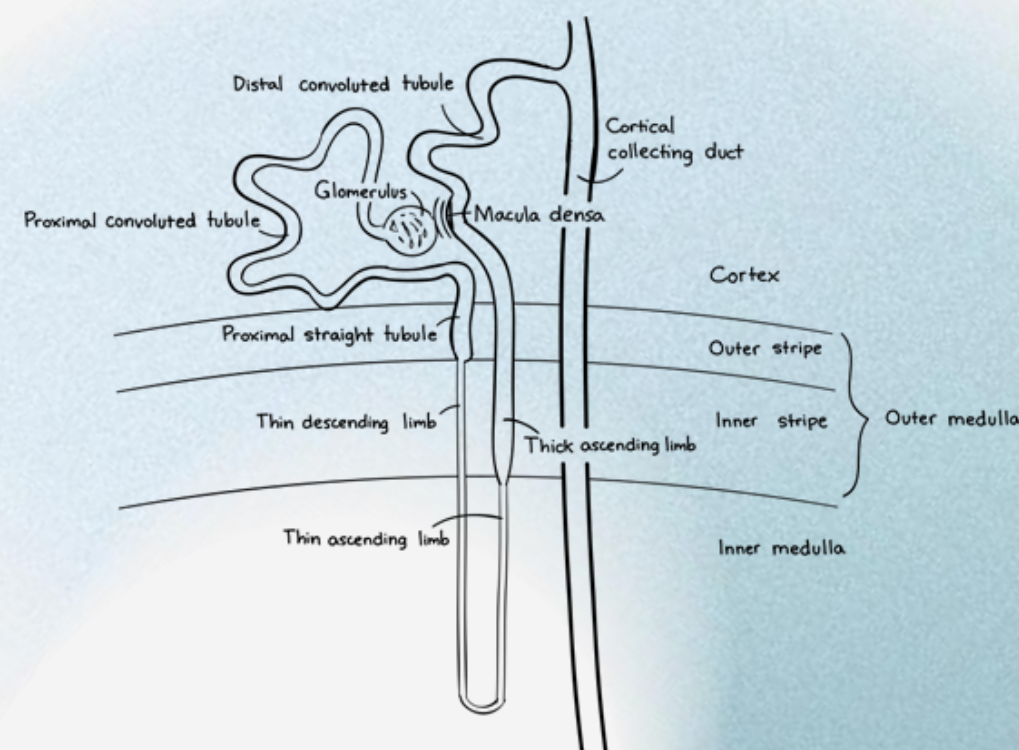
	Carbohydrate (g/L)	mEq/L			Osmolarity (mOSM/kg H ₂ O)
		Sodium	Potassium	Base (HCO ₃ ⁻)	
Oral rehydration solutions					
CeraLyte	40	70	20	10	235
Enfalyte	30	50	25	30	200
Pedialyte	25	45	20	30	250
Rehydralyte	25	75	20	30	310
WHO (1975)	20	90	30	30	310
WHO (2002)	13.5	75	20	30	245
Commonly Used Beverages (not appropriate for repletion therapy)					
Apple juice	100 to 150	3	20	0	700
Chicken broth	0	250	5	0	450
Colas	100 to 150	2	0.1	13	550
Gatorade	45	20	3	3	330
Ginger Ale	90	3.5	0.1	3.6	565
Tea	0	0	0	0	5

Graphic 67494 Version 4.0



Key Advantage: Standard Osmolarity

- A high total body water percentage (up to 80%), a large plasma volume relative to body weight with reduced buffering capacity, and immature renal ability to concentrate urine in infants
- Osmolarity: 245–250 mOsm/L (per WHO guidelines)
- Optimal osmolarity prevents further dehydration and electrolyte imbalance



Safety and Use in Pediatrics

- Prevention of hyponatremia risk and ...
- Has a very high safety margin
- Reduces risk of further dehydration during illness
- Accelerated rehydration
- Safe for sensitive groups





Indications

Rapid rehydration and electrolyte replenishment for:

- Diarrhea and vomiting
- Allergic gastrointestinal inflammations in neonates
- Fever, heavy sweating
- Burns
- Antibiotic-induced diarrhea
- Sports and heat exposure
- Lactation & Pregnancy

Unique Ingredients

- Promotes gut integrity and mucosal healing
 - Supports rapid resolution of diarrhea
- Superior absorption and GI compatibility compared to zinc gluconate





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Usage & Clinical Benefit

Clinical studies show reduced need for hospitalization and IV therapy in pediatric patients

The combination of Folimax and OneLyte is intended to accelerate the repair of intestinal villi and reduce inflammation of the intestinal epithelium



VITAX
HELIOS

Formulation & Packaging

- Ready-to-use bottles: 500 ml
- No need for dilution—just open and administer!
- The product can be stored at room temperature for up to 14 days
- Available in child-friendly **Green Apple Pomegranate** and **Original flavors**



Recommended Dosage

- Infants (6–12 months, 5.5–9 kg): 30–90 ml per episode
- Children (1–5 years): 60–120 ml per episode
- Older children & adults: As per physician's recommendation, based on dehydration severity

Infants	Children	adults
30 – 90 ml	60 – 120 ml	----



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Vitamin K-dependent proteins involved in bone and cardiovascular health (Review)

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Received August 30, 2017; Accepted February 13, 2018

DOI: 10.3892/mmr.2018.8940

Abstract. In postmenopausal women and elderly men, bone density decreases with age and vascular calcification is aggravated. This condition is closely associated with vitamin K2 deficiency. A total of 17 different vitamin K-dependent proteins have been identified to date. Vitamin K-dependent proteins are located within the bone, heart and blood vessels. For instance, carboxylated osteocalcin is beneficial for bone and aids the deposition of calcium into the bone matrix. Carboxylated matrix Gla protein effectively protects blood vessels and may prevent calcification within the vascular wall. Furthermore, carboxylated Gla-rich protein has been reported to act as an inhibitor in the calcification of the cardiovascular system, while growth arrest-specific protein-6 protects endothelial cells and vascular smooth muscle cells, resists apoptosis and inhibits the calcification of blood vessels by inhibiting the apoptosis of vascular smooth muscle cells. In addition, periostin may promote the differentiation, aggregation, adhesion and proliferation of osteoblasts. Periostin also occurs in the heart and may be associated with the reconstruction of heart function. These vitamin K-dependent proteins may exert their functions following γ -carboxylation with vitamin K, and different vitamin K-dependent proteins

review describes and briefly discusses several important vitamin K-dependent proteins that serve an important role in bone and the cardiovascular system. The results of the review suggest that the vascular calcification and osteogenic differentiation of vascular smooth muscle cells may be associated with the location of the bone and cardiovascular system during embryonic development.

Contents

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2. OC
3. MGP
4. GRP
5. Periostin
6. Gas6
7. Discussion and conclusions

1. Introduction



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International Congress Series

Volume 1297, March 2007, Pages 165-178



Role of vitamin K in the regulation of calcification

M. Kyla Shea, Sarah L. Booth  

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Abstract

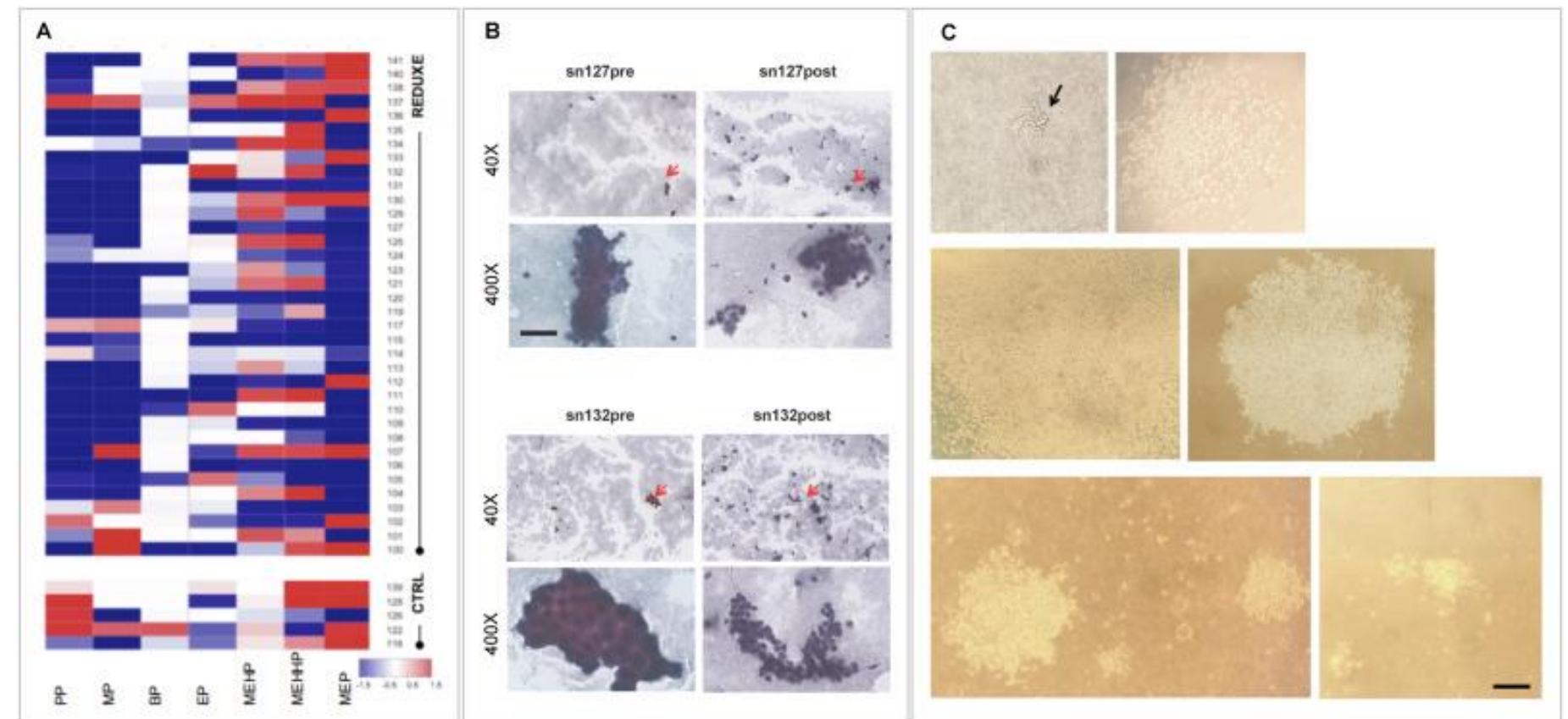
Observational studies are promising in terms of associations between vitamin K (either diet or biochemical measures) and bone health and other conditions of normal calcification in the elderly. The level of evidence from randomized, double-blind, placebo-controlled trials with phylloquinone is very limited. In contrast, there is strong evidence of a protective effect of menaquinone-4 in pharmacological doses on age-related bone loss and fracture risk. This effect appears to be enhanced by vitamin D



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- Manufactured by Alltone, UK
- This drop is one of the highest quality and safest drops of vitamin A and D in Iran
- Paraben free
- Gluten free
- good taste

Paraben



- A class of preservatives are very common in cosmetics and pharmaceutical products. Parabens have many derivatives and structures, most of which have shown good preservation properties. These compounds or their salts are mainly used for their antibacterial and antifungal properties.
- The association of parabens with some cancers (Breast cancer _ Lymphoma)
- The high sensitivity of children's immune system and the requirement for children's pharmaceutical products to be free of parabens

Original Article



Paraben Content in Adjacent Normal-malignant Breast Tissues from Women with Breast Cancer*

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Abstract

Objective Accumulation of estrogenic compounds and other carcinogens in normal breast tissues contributes to unpredictable breast cancer incidence during adolescence and throughout life. To assess the role of parabens in this phenomenon, the paraben content of adjacent normal-malignant breast tissues is measured in women with breast cancer living in Isfahan Province, Iran.

Methods Adjacent normal-malignant breast tissue samples were obtained from 53 subjects. The parabens including methyl-paraben (MePB), ethyl-paraben (EtPB), propyl-paraben (PrPB), and butyl-paraben (BuPB) were extracted from the sample supernatant and then subjected to gas chromatography analysis.

Results Some risk factors for breast cancer were stimulated by parabens in adjacent malignant-normal breast tissues among young and middle-aged women with breast cancer. We observed a significant association for dose-response pattern of MePB [OR = 98.34 (11.43–185.2), $P = 0.027$] for both ER+ and PR+ women and MePB [OR = 164.3 (CI: 112.3–216.3), $P < 0.001$] for HER2+ women than women with negative receptors. The risk of 95-fold increase in MePB dose and 164-fold increase in Σ PBs dose were significant for women with hereditary breast cancer in first-degree relatives.



Reduction of daily-use parabens and phthalates reverses accumulation of cancer-associated phenotypes within disease-free breast tissue of study subjects

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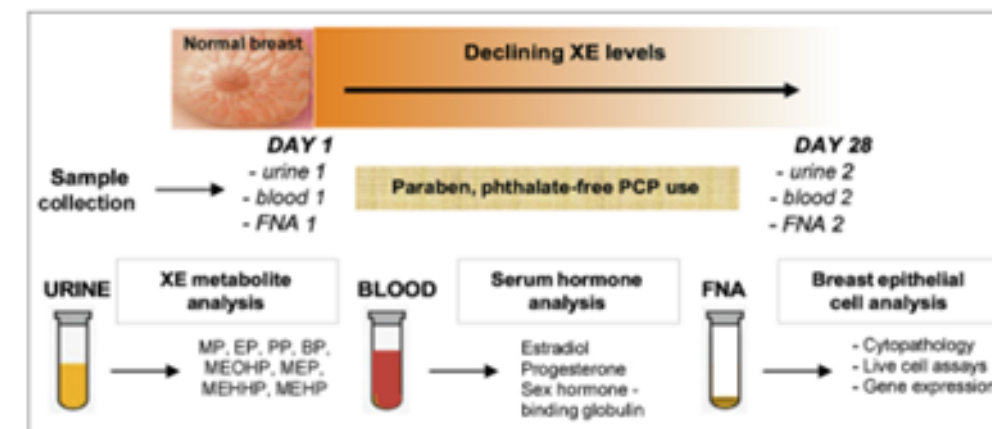
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^c Breast Cancer Over Time, San Francisco, CA, 94110, USA

HIGHLIGHTS

- The REDUXE intervention reveals the *in vivo* molecular impact of xenoestrogens within healthy human tissue.
- Substitution with paraben and phthalate-free product use reverses pro carcinogenic gene expression profiles.
- Estrogen-mediated functional signaling is normalized within post-REDUXE breast cells of participants.

GRAPHICAL ABSTRACT



ARTICLE INFO

Handling Editor: Jian-Ying Hu

ABSTRACT

Estrogenic overstimulation is carcinogenic to the human breast. Personal care products (PCPs) commonly contain xenoestrogens (XE), such as parabens and phthalates. Here, we identified the adverse effects of persistent

Thank
you

