

后生元的免疫调控功能研究 及临床实证

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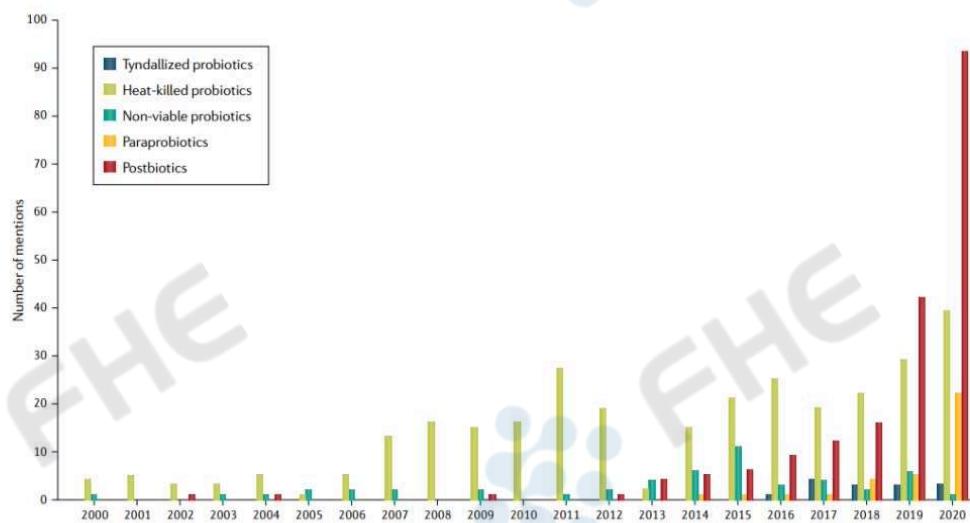
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后生元及其概念的演进

后生元概念的发展历史

过去 20 年间后生元相关研究的文章数量在不断增长¹



1998, Murosaki 在小鼠中证实了热灭活的 *L. plantarum* L-137 的免疫调控功效²

2011, Taverniti 首次提出了“副生元 /Paraprobiotic”³的概念，用以描述这些有功能的非活性细胞³

2013, Shenderov 首次提出了“代生元 /Metabiotics”⁴的概念，用于描述哪些有功能的益生菌的结构性组分⁴。同年，Tsilingiri 提出了“后生元 /Postbiotics”这个词⁵。

2017, “间歇法灭活的益生菌 /Tyndallized Probiotics”⁶在一篇综述文章中被首次提出，用以描述热灭活的益生菌⁶

1. Salminen, S., Collado, M.C., Endo, A. et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat Rev Gastroenterol Hepatol* 18, 649–667 (2021). <https://doi.org/10.1038/s41575-021-00440-6>
2. Murosaki S, Yamamoto Y, Ito K, Inokuchi T, Kusaka H, Ikeda H, Yoshikai Y (1998) Heat-killed *Lactobacillus plantarum* L-137 suppresses naturally fed antigen-specific IgE production by stimulation of IL-12 production in mice. *J Allergy Clin Immunol* 102:57–64
3. Taverniti, V.; Guglielmetti, S. The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: Proposal of paraprobiotic concept). *Genes Nutr.* 2011, 6, 261–274.
4. Shenderov, B.A. Metabiotics: Novel idea or natural development of probiotic conception. *Microb. Ecol. Health Dis.* 2013, 24, 20399.
5. Tsilingiri K, Rescigno M. Postbiotics: what else? *Benef Microbes.* 2013 Mar 1;4(1):101-7. doi: 10.3920/BM2012.0046. PMID: 23271068.
6. Piqué N, Berlanga M, Miñana-Galbis D. Health Benefits of Heat-Killed (Tyndallized) Probiotics: An Overview. *Int J Mol Sci.* 2019 May 23;20(10):2534. doi: 10.3390/ijms20102534. PMID: 31126033; PMCID: PMC6566317.

什么是后生元？

在 2021 年，国际益生菌和益生元科学协会（ International Scientific Association of Probiotics and Prebiotics/ISAPP ）将后生元定义为：

能赋予宿主**健康功效的灭活的微生物**和 / 或其组分的制剂

*Preparation of inanimate microorganisms and/or their components that confers a **health benefit** on the host.¹*

- **不是所有的死的微生物都能被称为后生元**
(需要经科学证实的健康功效)
- **纯化的微生物代谢产物不是后生元**
(如：β- 葡聚糖)
- **生产后生元的微生物不必是益生菌**
(如：酿酒酵母)

1. Salminen, S., Collado, M.C., Endo, A. et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat Rev Gastroenterol Hepatol* 18, 649–667 (2021). <https://doi.org/10.1038/s41575-021-00440-6>

Consensus Statement | Open Access | Published: 04 May 2021

The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics

Seppo Salminen, Maria Carmen Collado, Akihito Endo, Colin Hill, Sarah Lebeer, Eamonn M. M. Quigley, Mary Ellen Sanders, Raanan Shamir, Jonathan R. Swann, Hania Szajewska & Gabriel Vinderola

Nature Reviews Gastroenterology & Hepatology (2021) | Cite this article

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Abstract

In 2019, the International Scientific Association for Probiotics and Prebiotics (ISAPP) convened a panel of experts specializing in nutrition, microbial physiology, gastroenterology, paediatrics, food science and microbiology to review the definition and scope of postbiotics. The term 'postbiotics' is increasingly found in the scientific literature

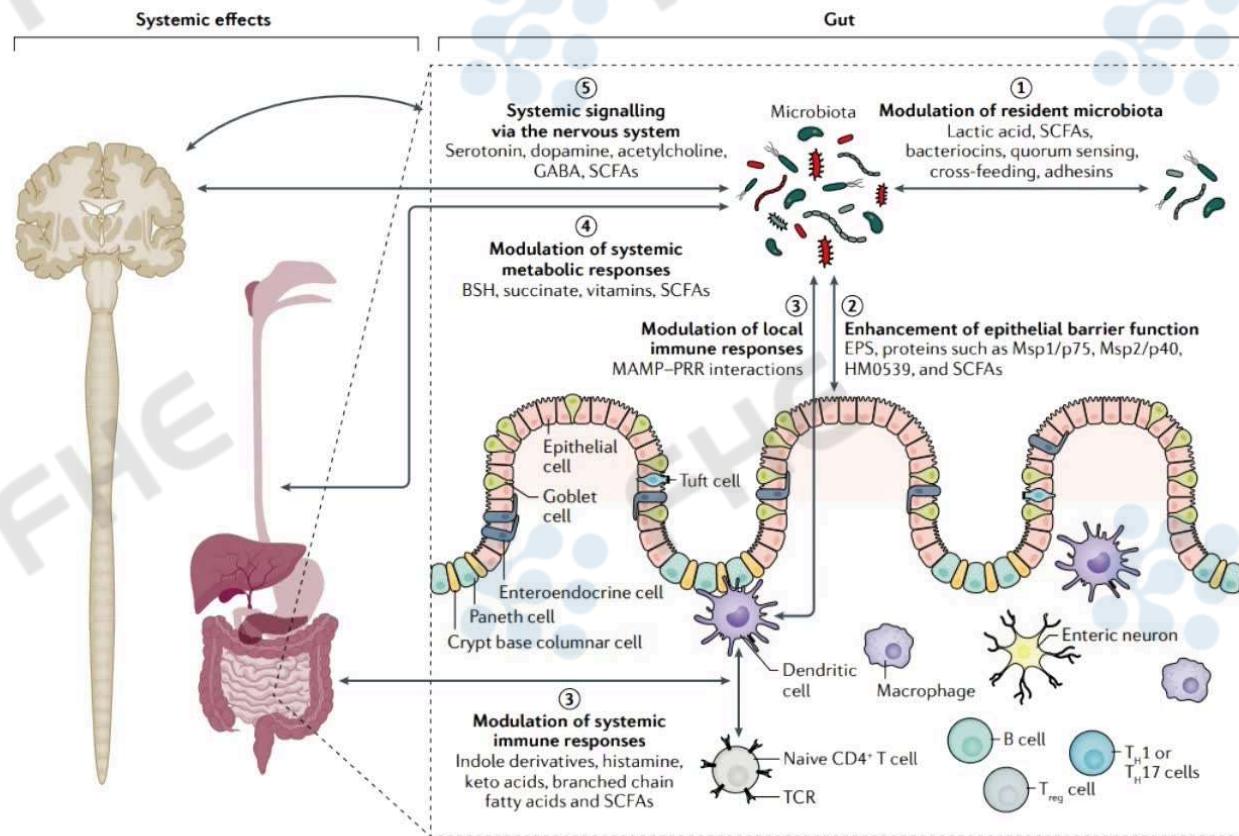
后生元与益生元和益生菌的异同

名词	年份	定义
Probiotics 益生菌	2014 年	<p>Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.¹</p> <p>当足量摄入时，能够赋予宿主健康功效的活的微生物</p>
Prebiotics 益生元	2017 年	<p>Substrates that are selectively utilized by host microorganisms and confer a health benefit.²</p> <p>能够被宿主微生物选择性利用，并赋予宿主健康功效的物质</p>
Postbiotics 后生元	2021 年	<p>Preparations of inanimate microorganisms and/or their components that confer a health benefit on the host.³</p> <p>能够赋予宿主健康功效的灭活的微生物和 / 或其组分的制剂</p>

1. Hill, C., Guarner, F., Reid, G. et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol* 11, 506–514 (2014). <https://doi.org/10.1038/nrgastro.2014.66>
2. Gibson, G., Hutkins, R., Sanders, M. et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol* 14, 491–502 (2017). <https://doi.org/10.1038/nrgastro.2017.75>
3. Salminen, S., Collado, M.C., Endo, A. et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat Rev Gastroenterol Hepatol* 18, 649–667 (2021). <https://doi.org/10.1038/s41575-021-00440-6>

后生元免疫调控功能的分子 / 生理基础

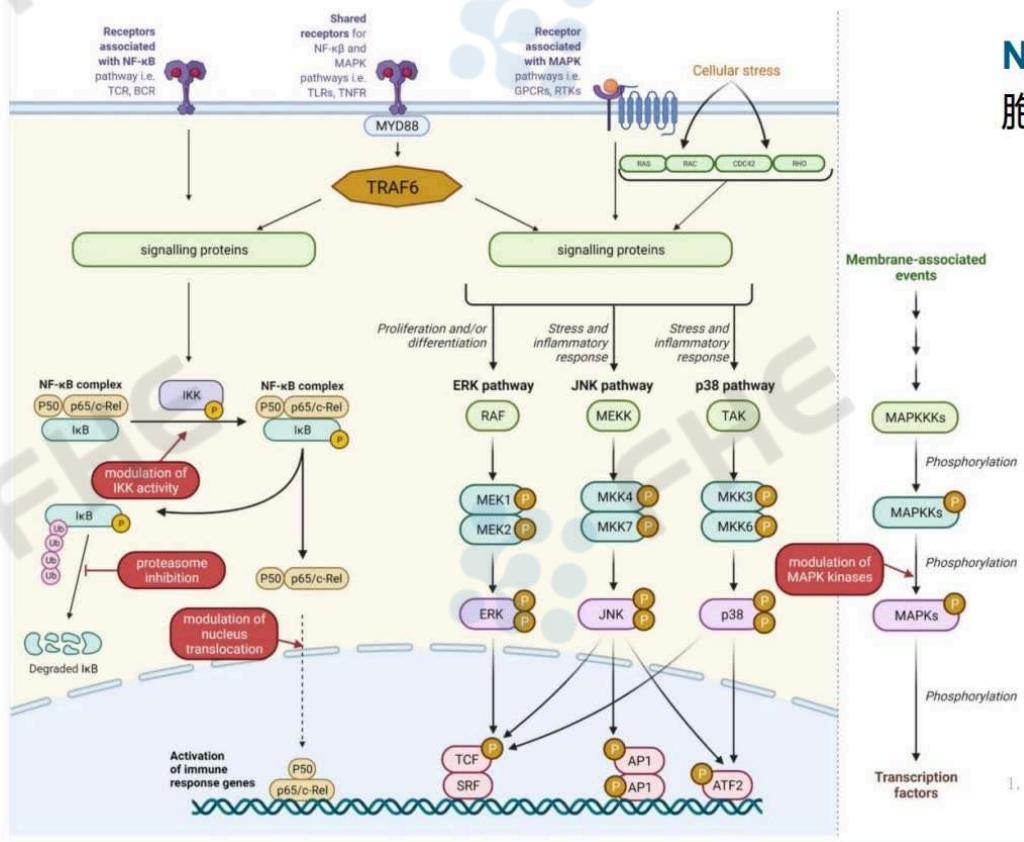
后生元可能的作用机理



1. 调节肠道微生态
2. 强化上皮屏障功能
3. 调节局部免疫应答
4. 调节系统免疫应答
5. 介导神经系统的信号转导

1. Salminen, S., Collado, M.C., Endo, A. et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat Rev Gastroenterol Hepatol* 18, 649–667 (2021).
<https://doi.org/10.1038/s41575-021-00440-6>

后生元免疫调控的分子基础



NF-κB 复合体和 MAPK 是炎症及免疫应答和细胞周期调控过程中至关重要的两条信号通路。¹

NF-κB signaling pathway:

- TCR—T-cell receptors,
- BCR—B-cell receptors,
- TLRs—toll-like receptors,
- TNFR—TNF α receptors superfamily,

MAPK signaling pathway:

- GPCRs—G protein coupled receptors,
- RTKs—receptor tyrosine kinase,
- TLRs—toll-like receptors,
- TNFR—TNF α receptors superfamily,

1. Jastrząb R, Graczyk D, Śledzicki P. Molecular and Cellular Mechanisms Influenced by Postbiotics. *Int J Mol Sci.* 2021 Dec;15(22):13475. doi: 10.3390/ijms222413475. PMID: 34948270; PMCID: PMC8707144.

后生元免疫调控的分子基础

Table 1. Postbiotic elements present in supernatants or in heat-killed/inactivated bacteria.

Postbiotics and Biologically Active Bacterial Byproducts	
Supernatant-Derived (CFS)	Cell-Derived (HKB)
<ul style="list-style-type: none">- Peptides:<ul style="list-style-type: none">- bacteriocins [29]- other peptides (quorum sensing, cyclic)- proteins:<ul style="list-style-type: none">- proteases i.e., lactocepin [30,31].- cell wall hydrolases i.e., p40 & p75 molecule [32]- serine protease inhibitors (i.e., serpin) [33]- other extracellular proteins [34,35]- lipids:<ul style="list-style-type: none">- SCFA (i.e., butyrate [36]- conjugated linoleic acid (CLA) [37]- other less studied fatty acid derivatives- other exopolysaccharides- small organic molecules- lactic acid- D-amino acids [38]- indole derivatives [39,40]- other unknown small molecules- vitamins/cofactors [27]- inorganic molecules i.e., polyphosphate [41,42]- fermentation products * [43]	<ul style="list-style-type: none">- S-layer proteins [42–48]- lipoteichoic acid (LTA)—as derivative of cell wall component [49]- peptidoglycan-derived muropeptides from cell wall [50]- polysaccharides from cell wall- galactose-rich polysaccharides [capsular PS] [51–59]- intracellular proteins

* For fermentation products see [58,59].

Lactobacillus plantarum 10hk2 发酵产生的一种肽能够抑制 LPS 诱导的 NF-κB 的激活和 p38 MAPK 的磷酸化，并诱导 IL-10 的产生。²

LGG 的 DNA 能够促进 HT-29 细胞中 TLR9 的表达，并减少 IκB 的降解，从而抑制 TNF-α 诱导的 NF-κB 的激活及其介导的 IL-8 的产生。

3

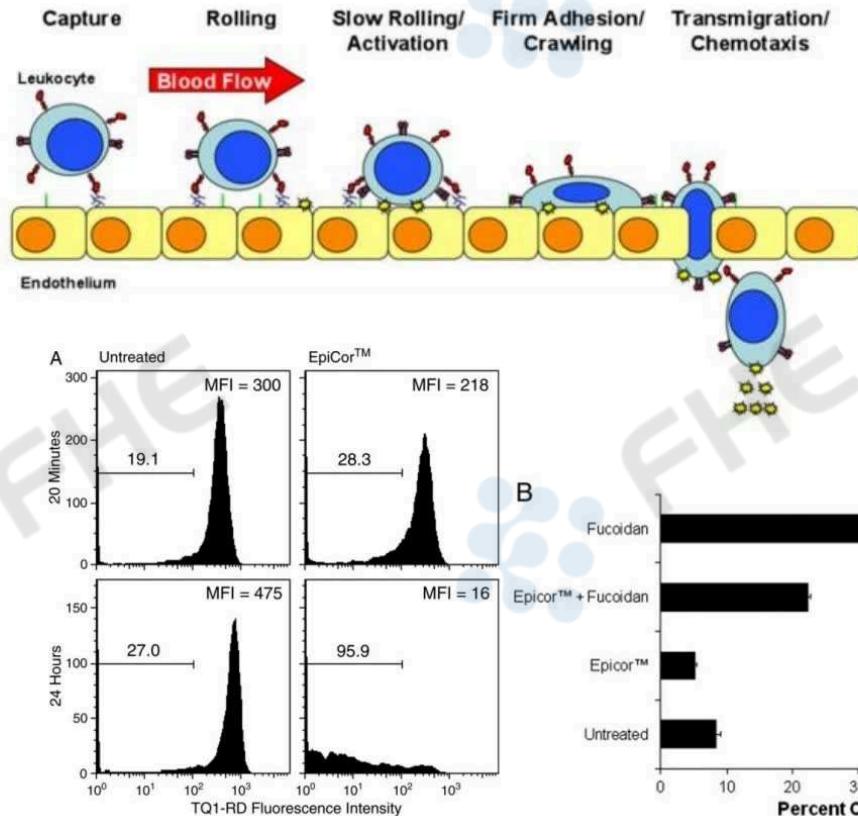
1. Jastrząb R, Graczyk D, Siedlecki P. Molecular and Cellular Mechanisms Influenced by Postbiotics. *Int J Mol Sci.* 2021 Dec 15;22(24):13475. doi: 10.3390/ijms222413475. PMID: 34948270; PMCID: PMC8707144.

2. Chon H, Choi B, Jeong G, Lee E, Lee S. Suppression of proinflammatory cytokine production by specific metabolites of *Lactobacillus plantarum* 10hk2 via inhibiting NF-κB and p38 MAPK expressions. *Comp Immunol Microbiol Infect Dis.* 2010 Dec;33(6):e41-9. doi: 10.1016/j.cimid.2009.11.002. Epub 2009 Dec 1. PMID: 19954847.

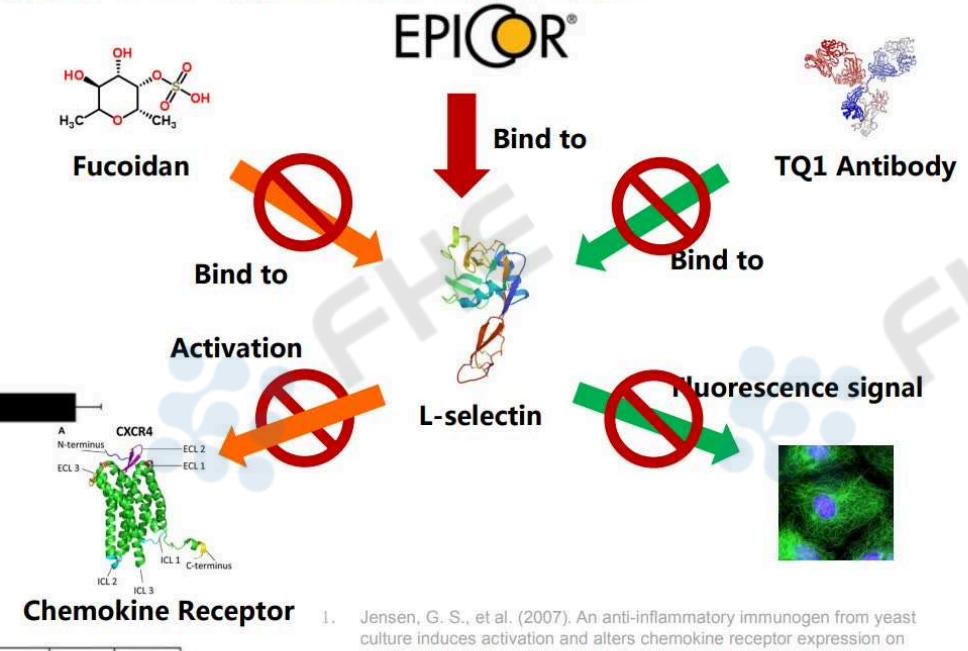
3. Ghadimi D, Vrese Md, Heller KJ, Schrezenmeir J. Effect of natural commensal-origin DNA on toll-like receptor 9 (TLR9) signaling cascade, chemokine IL-8 expression, and barrier integrity of polarized intestinal epithelial cells. *Inflamm Bowel Dis.* 2010 Mar;16(3):410-27. doi: 10.1002/ibd.21057. PMID: 19714766.

酵母后生元免疫调控功能的临床实证

基于 L-selectin 信号通路的炎症调节作用(*in vitro*)

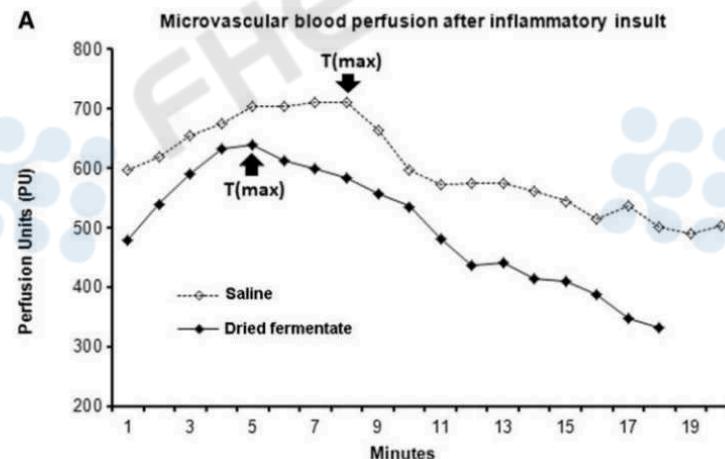
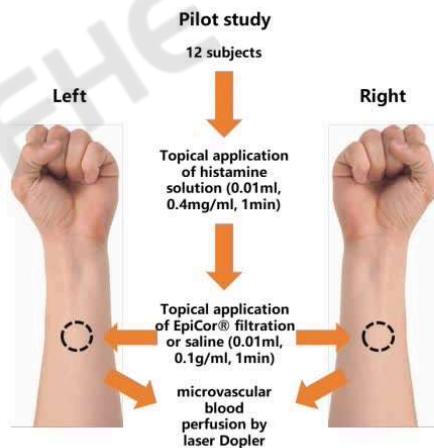
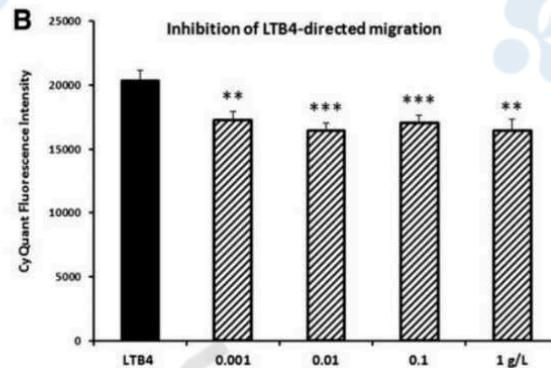
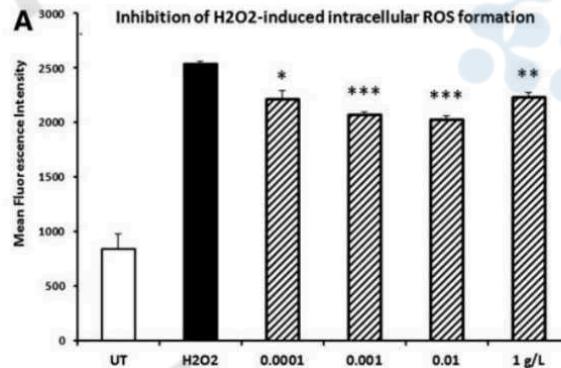


非活性食用酵母后生元 (EpiCor®) 能够通过抑制依赖 L-selectin 信号通路¹的淋巴细胞的迁移来缓解炎症反应



- Jensen, G. S., et al. (2007). An anti-inflammatory immunogen from yeast culture induces activation and alters chemokine receptor expression on human natural killer cells and B lymphocytes in vitro. Nutr Res 27 (6), 327-35.

抑制炎症细胞迁移，并缓解局部皮肤炎症(人体实验)



还能够观察到 EpiCor® 对 H₂O₂ 诱导的 ROS 产生的抑制作用¹.

体外实验中观察到 EpiCor® 能够抑制炎症细胞向趋化因子白三烯 B4 的迁移¹;

临床实验表明 EpiCor® 能够缓解组胺诱导的皮肤炎症，主要表现为局部毛细血管血流灌注的减少：

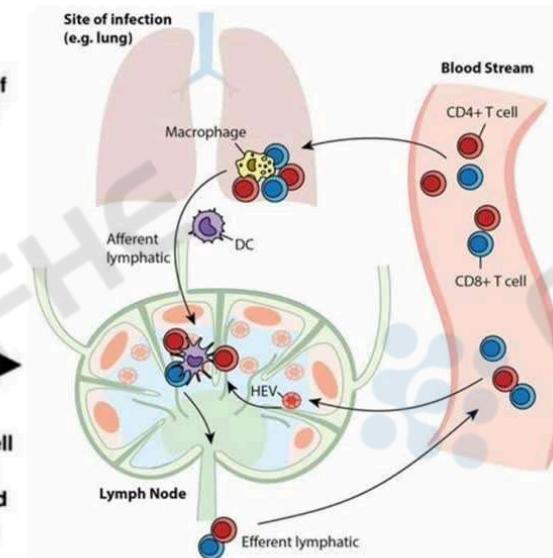
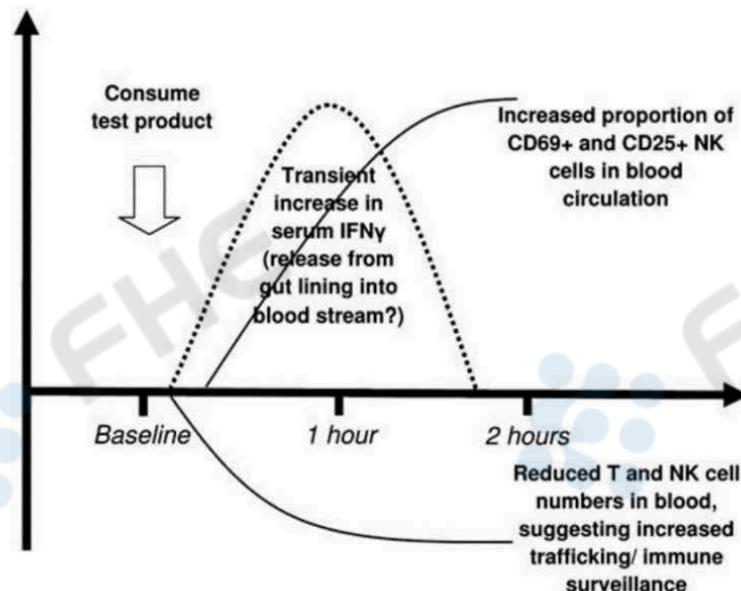
- ✓ 最大血流灌注时间 Tmax 显著缩短
- ✓ Tmax 后的曲线斜率显著变陡峭

1. Jensen, G. S., et al. (2015). Anti-inflammatory properties of a dried fermentate in vitro and in vivo. J Med Food 18(3), 378-84.

促进淋巴细胞归巢，快速激活免疫系统(人体实验)

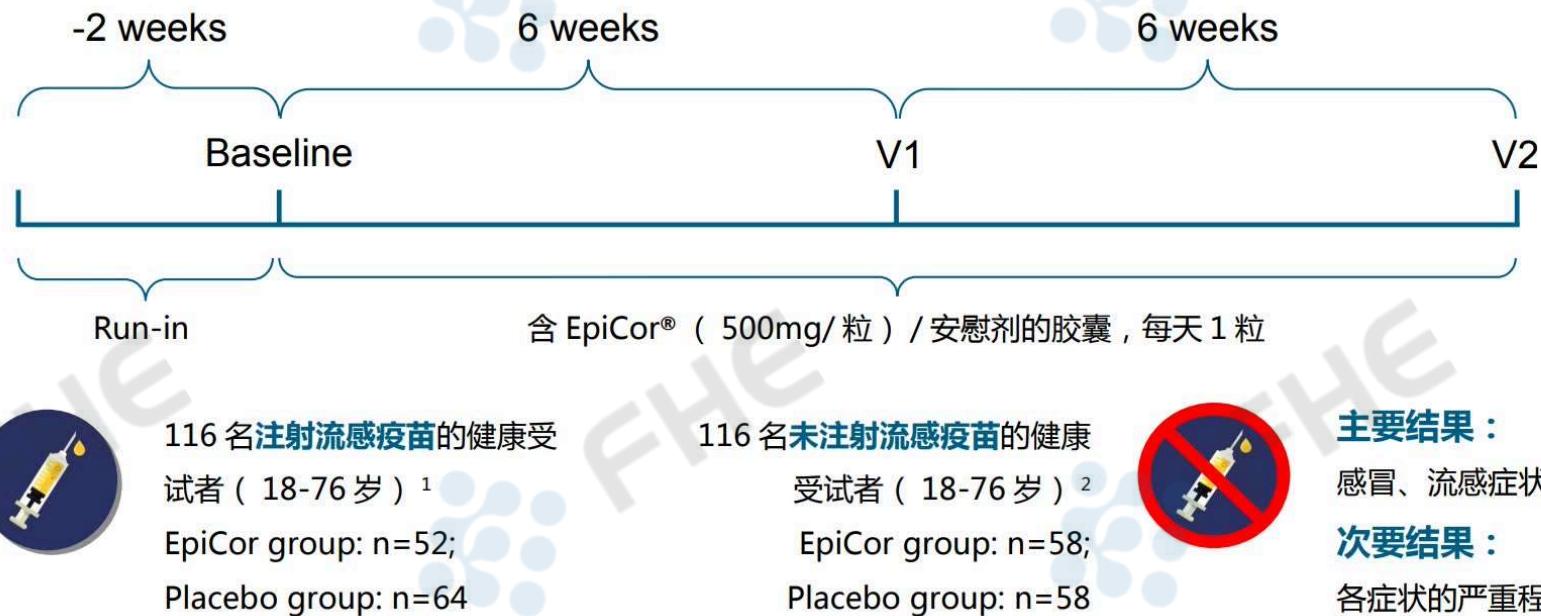
1项针对 12 名受试者的临床实验表明¹，在服用 EpiCor 1-2 小时之后能够引发机体的快速免疫反应，暗示了 EpiCor 作用更加直接且快速的特点。

- ✓ EpiCor® 组外周血样本中淋巴细胞的数量显著降低 (CD3+ T cells , p=0.01 ; CD3-CD56+ NK cells , p=0.05) ；
- ✓ EpiCor® 组淋巴细胞表面免疫相关受体的表达水平显著升高 (CD25 , p=0.05 ; CD69 , p=0.05)



1. Jensen, G. S., et al. (2010). Antioxidant bioavailability and rapid immune-modulating effects after consumption of a single acute dose of a high-metabolite yeast immunogen: results of a placebo-controlled double-blinded crossover pilot study. J Med Food 14, 1002–10.

增强机体免疫力，缓解感冒 / 流感症状(RCT)



1. Moyad, M. A., et al. (2010). Immunogenic yeast-based fermentate for cold/flu-like symptoms in nonvaccinated individuals. *J Altern Complement Med* 16 (2), 213-8.
2. Moyad, M. A., et al. (2009). Immunogenic yeast-based fermentation product reduces allergic rhinitis-induced nasal congestion: a randomized, double-blind, placebo-controlled trial. *Adv Ther* 26 (8), 795-804.

主要结果：

感冒、流感症状的发生率和持续时间

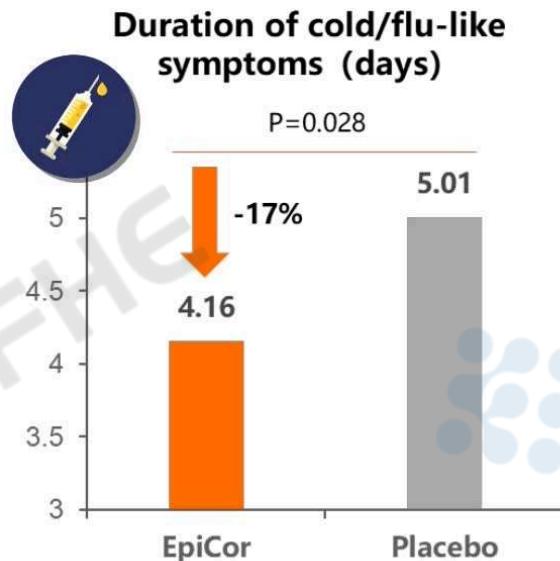
次要结果：

各症状的严重程度

症状包括：头痛、全身疼痛、疲劳、虚弱、鼻塞、鼻腔引流、喉咙痛、咳嗽、声音嘶哑、胸部不适、发冷、发烧

增强机体免疫力，缓解感冒 / 流感症状(RCT)

2项独立的分别针对注射流感疫苗（n=116）和没有注射流感疫苗（n=116）的人群的临床实验，以及1项针对花粉过敏人群的临床实验证明，EpiCor能够增强受试者的免疫功能以对抗感冒，并表现出对疫苗的增效作用^{1, 2}



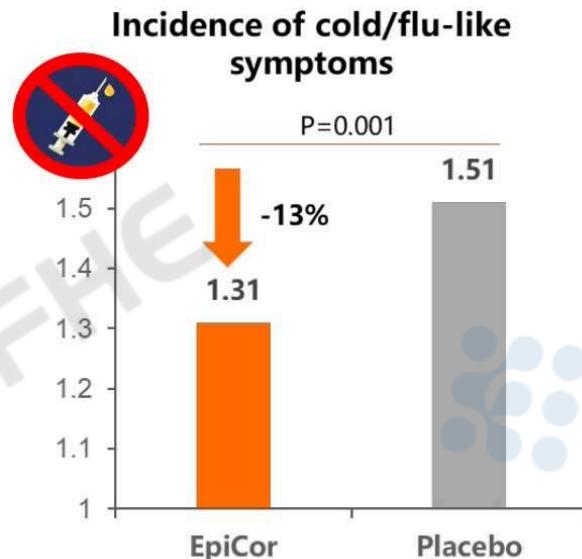
主要结果：

- EpiCor® 组的感冒和流感症状的发生率显著降低（从 1.42 降低到 1.26，p=0.011），
- 症状持续时间显著缩短（从 5.01 天缩短到 4.16 天，p=0.028）；
- EpiCor® 组在一些流感具体症状上也被显著改善，如声音嘶哑（p=0.008）和鼻塞（p=0.008）症状的发生率显著降低，虚弱无力状态（p=0.008）的持续时间显著缩短；

1. Moyad, M. A., et al. (2010). Immunogenic yeast-based fermentate for cold/flu-like symptoms in nonvaccinated individuals. *J Altern Complement Med* 16 (2), 213-8.
2. Moyad, M. A., et al. (2009). Immunogenic yeast-based fermentation product reduces allergic rhinitis-induced nasal congestion: a randomized, double-blind, placebo-controlled trial. *Adv Ther* 26 (8), 795-804.

增强机体免疫力，缓解感冒 / 流感症状(RCT)

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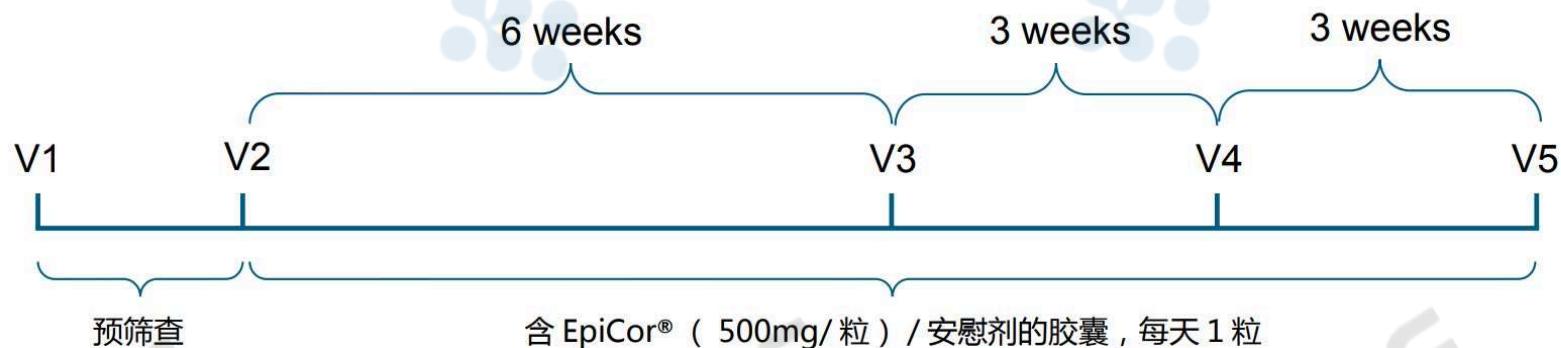
主要结果：

- EpiCor® 组的感冒和流感症状的发生率显著降低（从 1.51 降低到 1.31 , p=0.001 ）；
- 但 EpiCor® 组缩短症状持续时间的效果不显著 (p=0.1) ；
- EpiCor® 组 11 种特定感冒 / 流感症状中的 10 种症状（虚弱无力除外）的发生率被降低，且 9 种症状（发冷和胸部不适除外）的持续时间被缩短。

1. Moyad, M. A., et al. (2010). Immunogenic yeast-based fermentate for cold/flu-like symptoms in nonvaccinated individuals. J Altern Complement Med 16 (2), 213-8.

2. Moyad, M. A., et al. (2009). Immunogenic yeast-based fermentation product reduces allergic rhinitis-induced nasal congestion: a randomized, double-blind, placebo-controlled trial. Adv Ther 26 (8), 795-804.

平衡免疫系统，缓解过敏症状(RCT)



96 名经皮肤测试对草过敏的受试者¹

EpiCor group: n=48;
Placebo group: n=48

各检测点的测试及数据收集：

V1 : 签署知情同意书，标准血液检测，皮肤过敏性测试；

V2 : 用药历史信息收集，血液及唾液样本收集，派发 RQLQ 及症状日志；

V3 : 血液及唾液样本收集，症状日志及 RQLQ 数据收集；

V4/5 : 血液及唾液样本收集⁽¹⁾, 症状日志及 RQLQ 数据

收集，及鼻腔样本收集

主要结果：

症状的平均持续总天数和平均严重程度

鼻部症状：

鼻塞，流鼻涕，打喷嚏

眼部症状：

流眼泪，眼部瘙痒

1. Moyad, M. A., et al. (2008). Effects of a modified yeast supplement on seasonal allergic rhinitis symptoms in adults. *Journal of Allergy and Clinical Immunology*, 121(5), 1121-1127.

平衡免疫系统，缓解过敏症状(RCT)

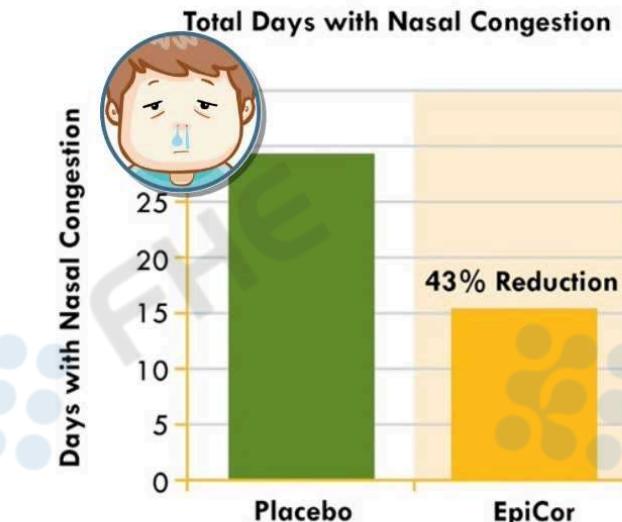
主要结果：

相较于安慰剂组，
在花粉浓度最高的前 6 周，EpiCor® 对过敏性鼻炎症状的改善效
果最为明显：

- 鼻塞的严重程度显著 **-14%** ($p=0.04$)；
- 流涕的严重程度显著 **-19%** ($p=0.005$)；
- 鼻塞症状持续时间显著 **-43%** ($p=0.04$)；

相较于安慰剂

- 鼻腔分泌液中**淋巴细胞数量**显著降低 (V4, $p=0.05$; V5,
 $p=0.03$);
- **唾液 IgA 分泌量**显著升高 ($p=0.03$)。



1. Moyad, M. A., et al. (2008). Effects of a modified yeast supplement on cold/flu symptoms. Urol Nurs 28 (1), 50-5.

小结

- “后生元”作为继“益生菌”和“益生元”之后的全新概念，正在受到越来越多研究者和市场的关注。
- 通过特定的有益代谢产物或结构性细胞组分，后生元能够直接或间接作用于机体免疫系统，并发挥调节作用。
- 作为酿酒酵母来源的后生元，EpiCor®具有炎症调节和平衡机体免疫系统的作用。

感谢您的聆听！

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