



Phytonutrients: The Next Generation

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Presentation overview

- What is the role of phytonutrients in the diet?
 - Background and history
 - Humans & animals
- How has the science evolved since the first applications in animal production?
 - Insights and shifts from first to second generation paradigms
- Current challenges limiting progress
- Next generation phytonutrients: a new paradigm for the future

Newsflash: diet influences health!



Harvard Women's Health Watch; June 2018

Traditional Medicine: age-old wisdom

"Traditional medicine refers to the theories, beliefs and experiences used in the maintenance of health and improvement or treatment of health conditions... often termed alternative or complementary medicine in many countries... used as primary health care in some countries."

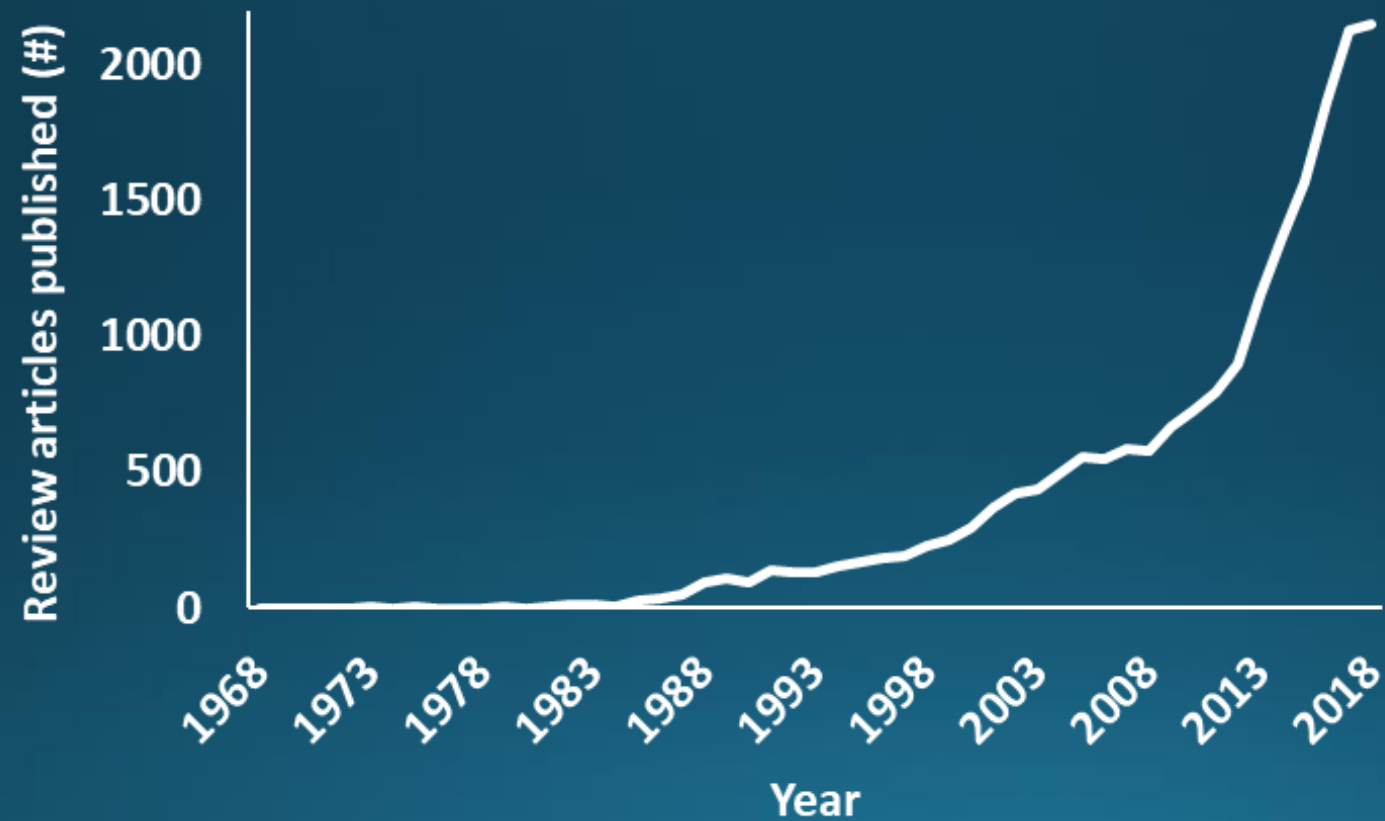
Evidence-Based Complementary and Alternative Medicine

TABLE 1: Some important texts in the historical development of traditional Chinese medicine

Lectures	Issued date	Total	Plant
52 Bing-Fang	200 BCE	247	115
Shen-Nong-Ben-Cao-Jing	202 BCE–220	365	252
Xin-Xiou-Ben-Cao	659	850	635
Zheng-Lei-Ben-Cao	1082	1,746	1,151
Ben-Cao-Gang-Mu	1596	1,892	1,094
Zhong-Yao-Da-Ci-Dian	1977	5,767	4,773
Zhong-Hua-Ben-Cao	1999	8,980	7,815
Chinese Pharmacopoeia	2010	2,165	680

Pan et al., 2014.

Traditional Medicine: the new chic!



West catches up with East...finally!



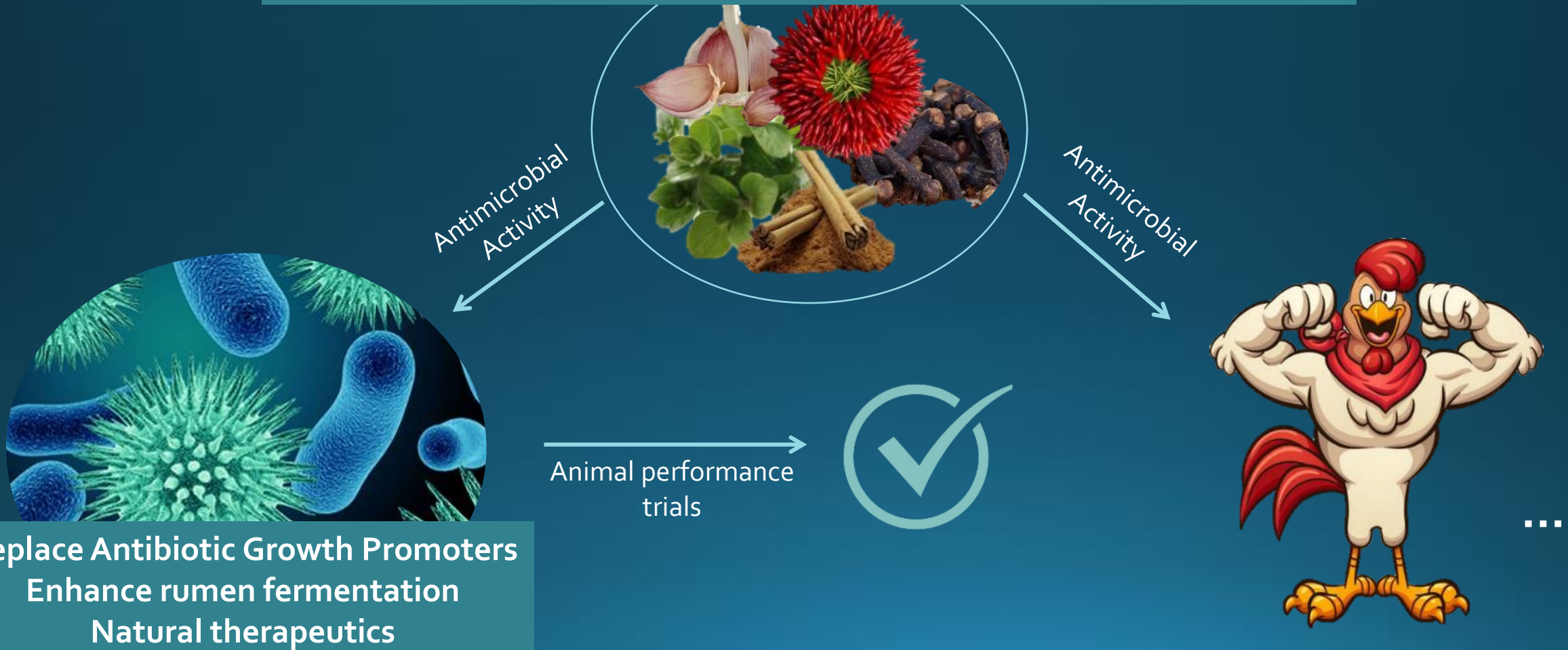
*"Traditional medicine can be used as an input to "modern" pharmaceutical research, but also as source of effective treatments in its own right...
...consider ways in which the potential of traditional medicine for providing affordable treatments could be better realised."*

Phytonutrients in human medicine

- The concept that phytonutrients have a direct impact on the health of the animal that ingests the plants is now validated and accepted by the Scientific and Medical communities
 - Mechanisms increasingly clear
 - Preventative & dietary therapies actively explored
 - Global organizations recognize the potential: WHO
- What about health and disease in production animals?

First generation phytonutrients in animal production

Most of the industry today still works under this paradigm.



The dangers of oversimplification & lack of science



- Phytonutrients are good *because* they kill bacteria
- Phytonutrients that do not kill bacteria are not of interest
- Phytonutrients kill bacteria, so they can be used as therapeutics
- Phytonutrients kill bacteria, so they could contribute to antibiotic resistance



Unhappy customers



Building understanding based on science



PERFORMANCE ENHANCING
EFFECTS



BACTERIAL KILLING
EFFECTS

>10 ppm

200 ppm

400 ppm

>800 ppm

PHYTONUTRIENT CONCENTRATION

What can explain the performance response?

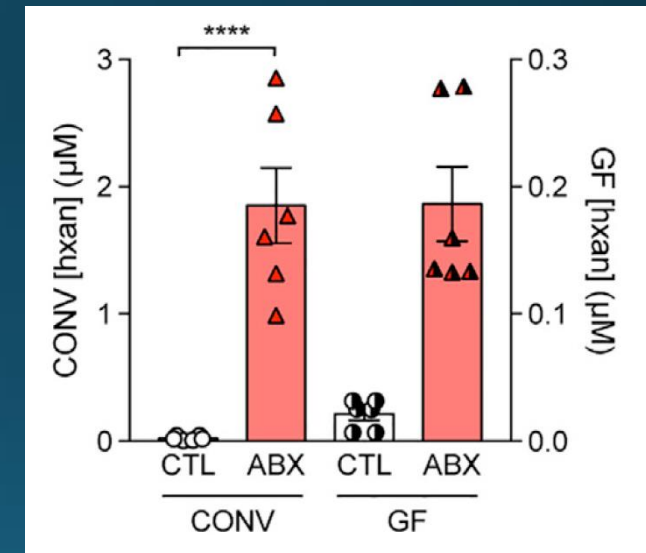
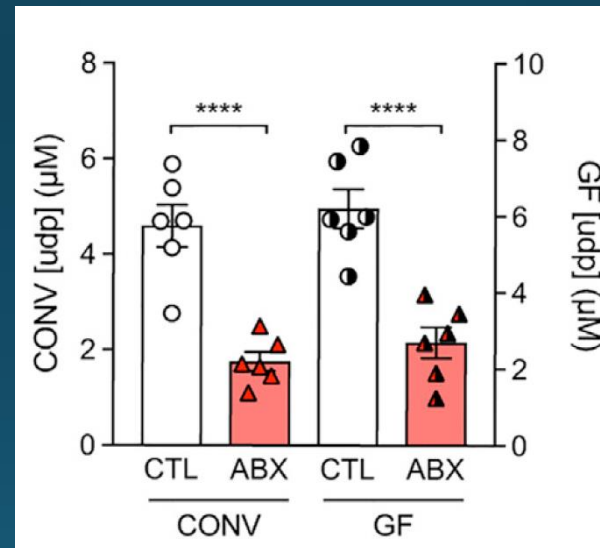
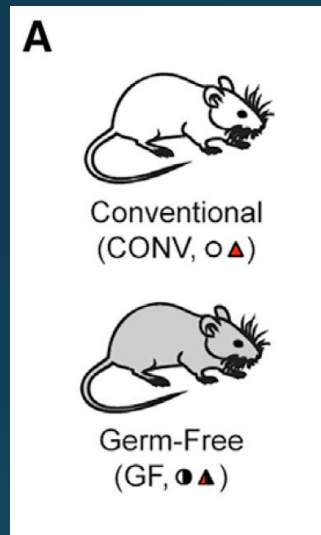
It must be due to effects on gut microbes!



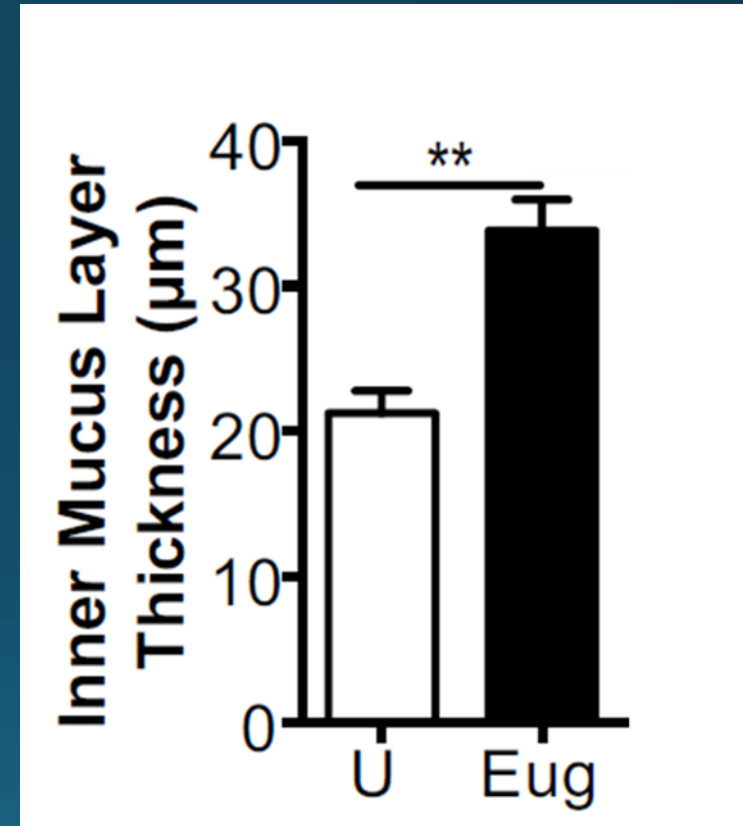
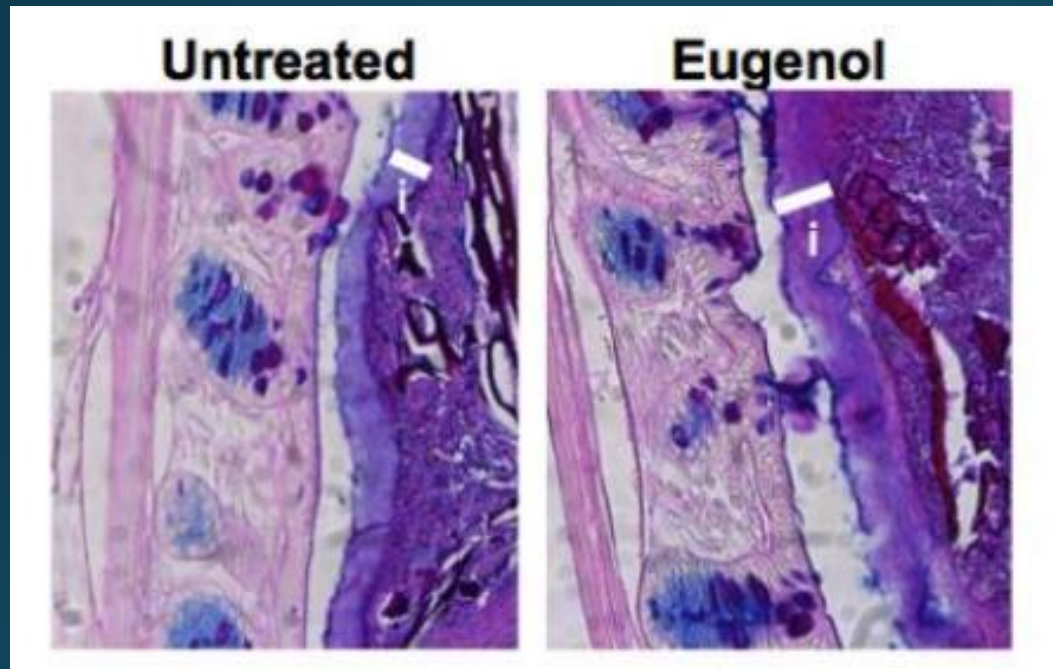
Same explanation used for antibiotic growth promoters...

Building understanding based on science

Antibiotic Treatment Elicits Microbiome-Independent Changes in Host Metabolites



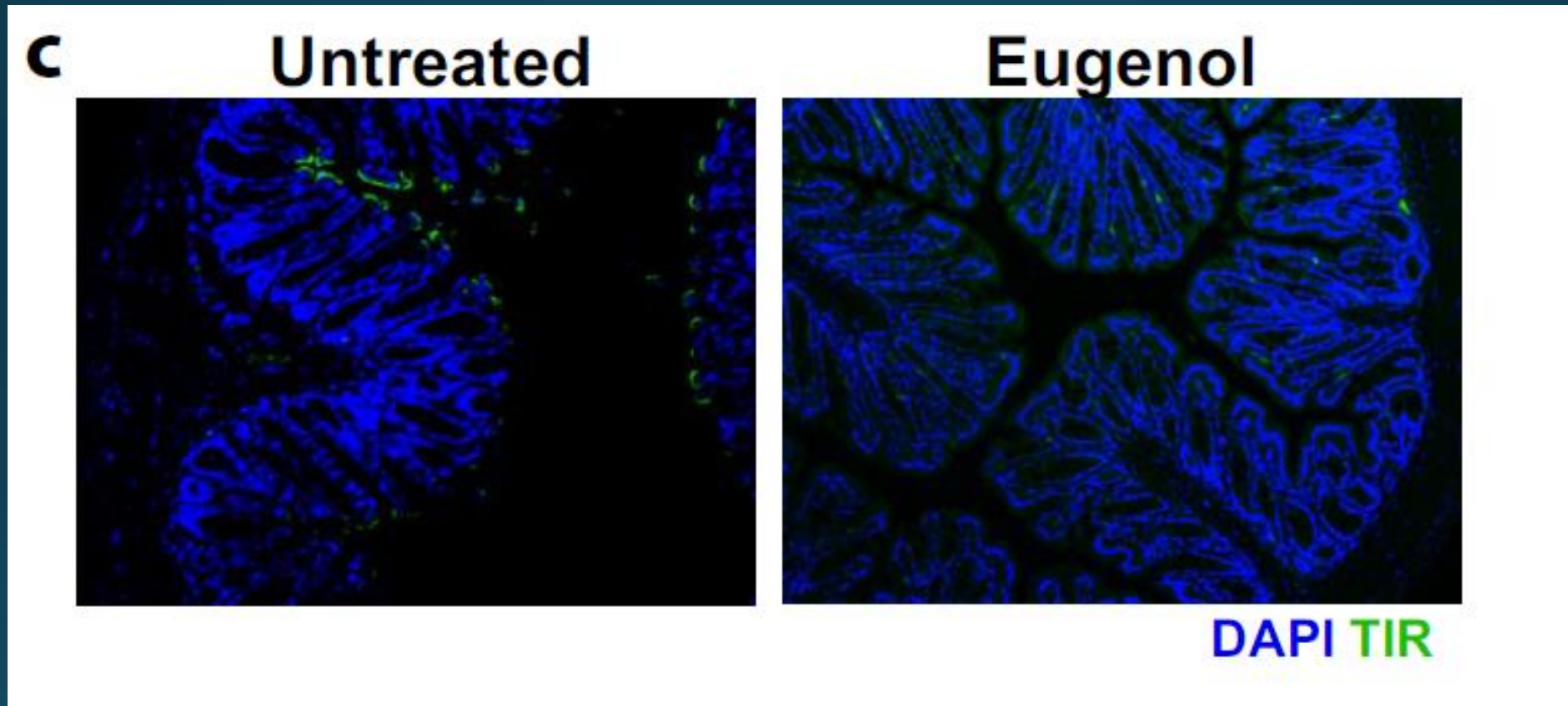
Building understanding based on science



Eugenol (3 ppm) improves intestinal structure



Building understanding based on science



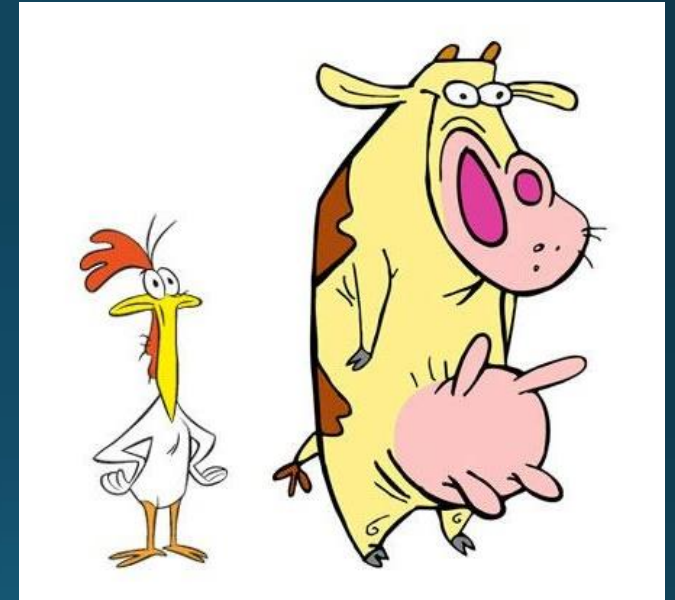
Eugenol (3 ppm) prevents adhesion of bacteria in the colon...



Second generation phytonutrients in animal production



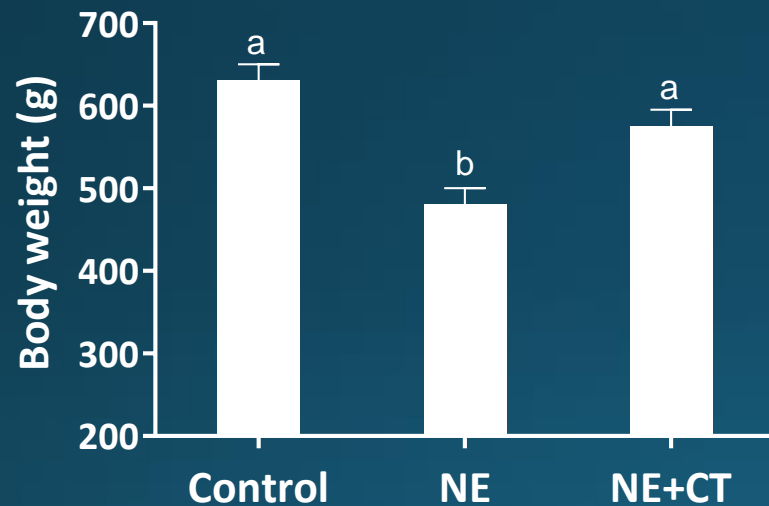
**It's not the bugs, it's
the Hosts!!!**



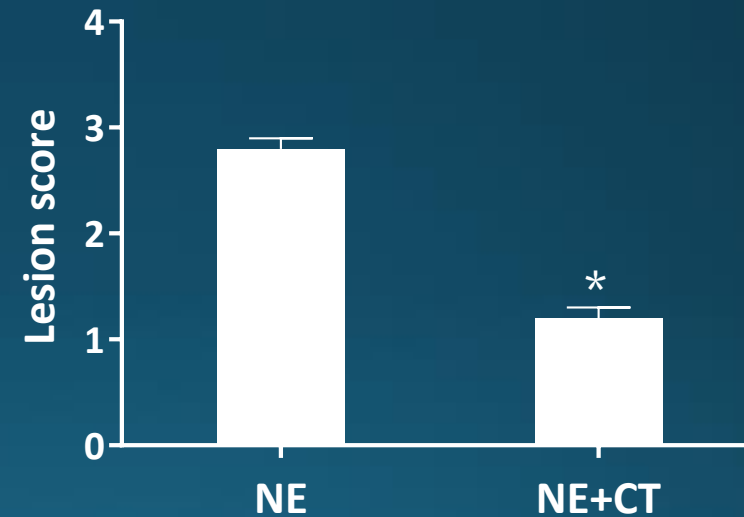
Host-mediated effects of phytonutrients in production animals: pioneer research



Improved performance



Improved gut health

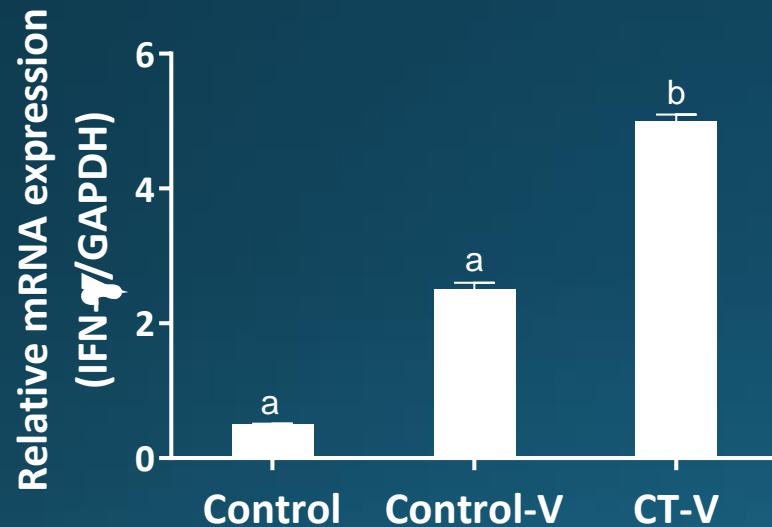


NE = necrotic enteritis challenge; CT = capsicum & turmeric oleoresins (4 ppm); Lee et al., 2013 Brit. J. Nut.

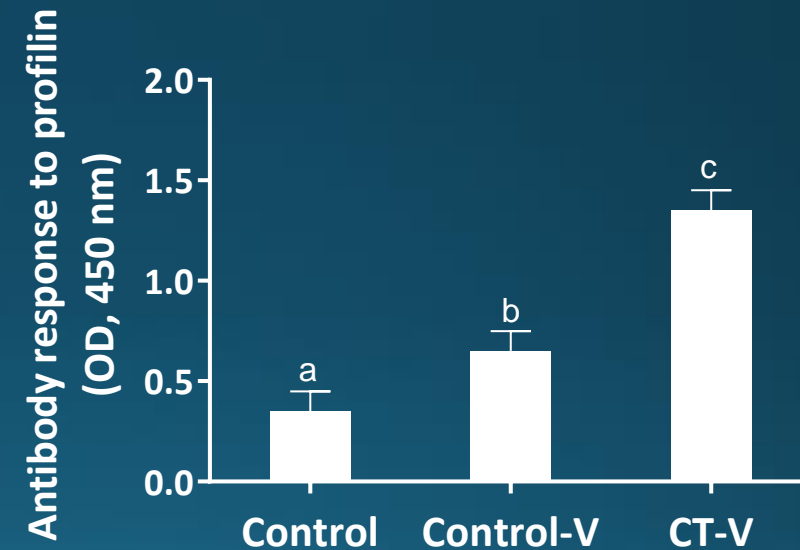
Host-mediated effects of phytonutrients in production animals: pioneer research



Altered immune gene expression in the intestine



Increased vaccination response



Host-mediated effects of phytonutrients in production animals: pioneer research



"These results provide new information concerning the molecular mechanisms involved in dietary modulation of host immunity, physiology, and metabolism.

Future studies based on these results will contribute to comprehensive understanding of the molecular mechanism of phytonutrients in the chicken digestive tract and will facilitate the development of novel dietary strategies to immunomodulate host response in normal and disease states."

Kim et al., 2010. Poultry Sci.

Host-mediated effects of phytonutrients in production animals: pioneer research



The gut as a sensory organ

John B. Furness, Leni R. Rivera, Hyun-Jung Cho, David M. Bravo and Brid Callaghan

Abstract | The gastrointestinal tract presents the largest and most vulnerable surface to the outside world. Simultaneously, it must be accessible and permeable to nutrients and must defend against pathogens and potentially injurious chemicals. Integrated responses to these challenges require the gut to sense its environment, which it does through a range of detection systems for specific chemical entities, pathogenic organisms and their products (including toxins), as well as physicochemical properties of its contents. Sensory information is then communicated to four major effector systems: the enteroendocrine hormonal signalling system; the innervation of the gut, both intrinsic and extrinsic; the gut immune system; and the local tissue defence system. Extensive endocrine–neuro–immune–organ–defence interactions are demonstrable, but under-investigated. A major challenge is to develop a comprehensive understanding of the integrated responses of the gut to the sensory information it receives. A major therapeutic opportunity exists to develop agents that target the receptors facing the gut lumen.

Furness, J. B. *et al.* *Nat. Rev. Gastroenterol. Hepatol.* advance online publication 24 September 2013; doi:[10.1038/nrgastro.2013.180](https://doi.org/10.1038/nrgastro.2013.180)

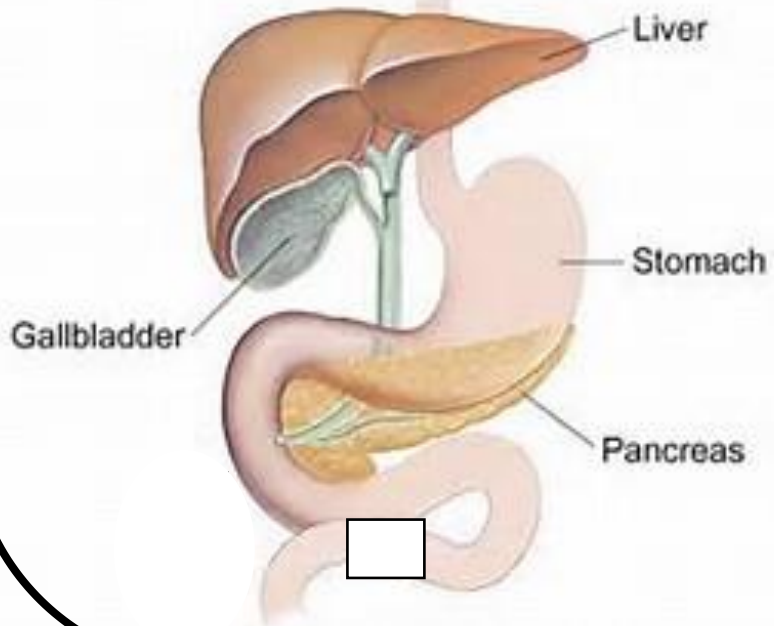
nature
REVIEWS

GASTROENTEROLOGY
& HEPATOLOGY



DECREASED INFLAMMATION + INCREASED ABSORPTION

IMPROVED PERFORMANCE

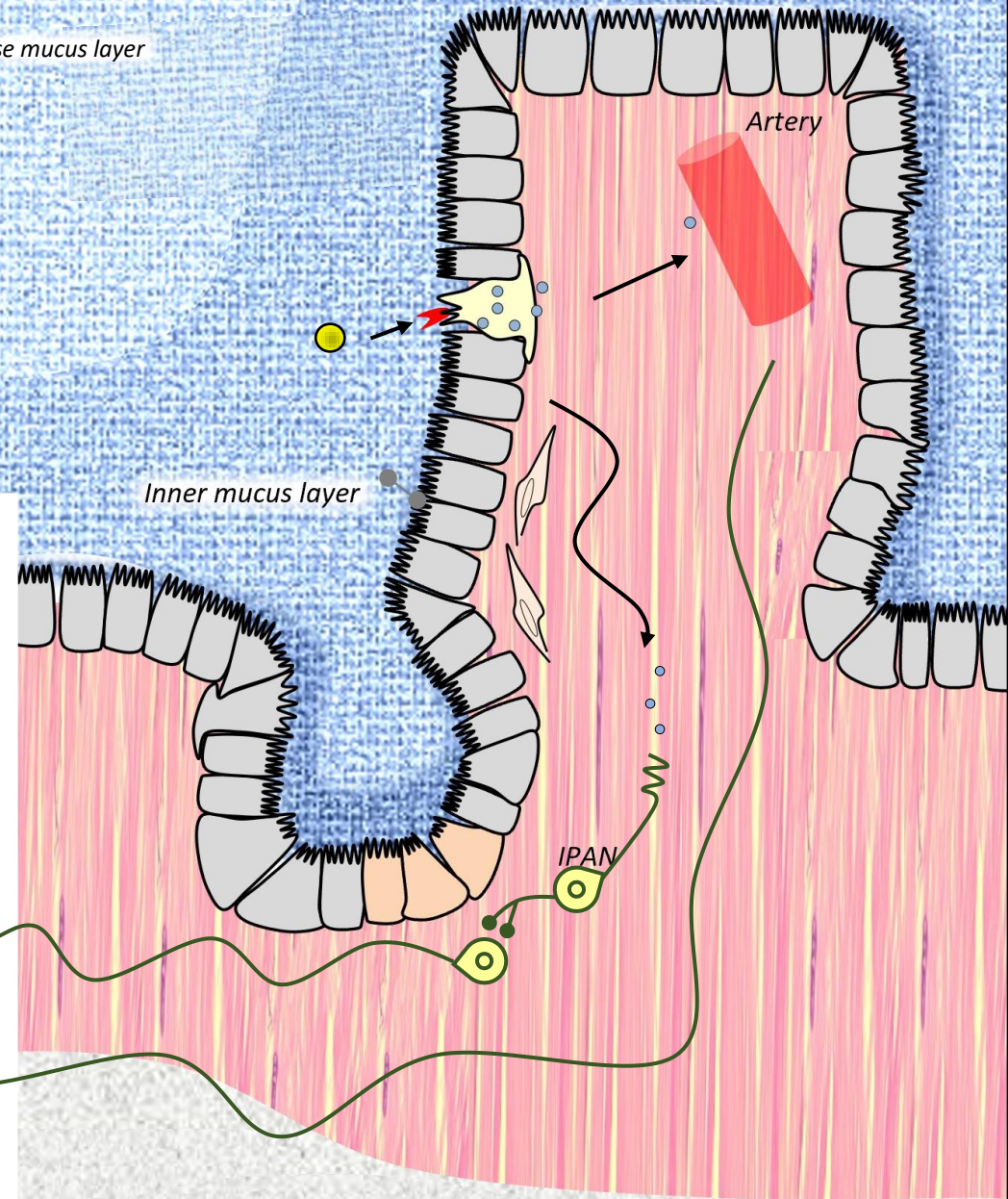


Loose mucus layer

Artery

Inner mucus layer

IPAN

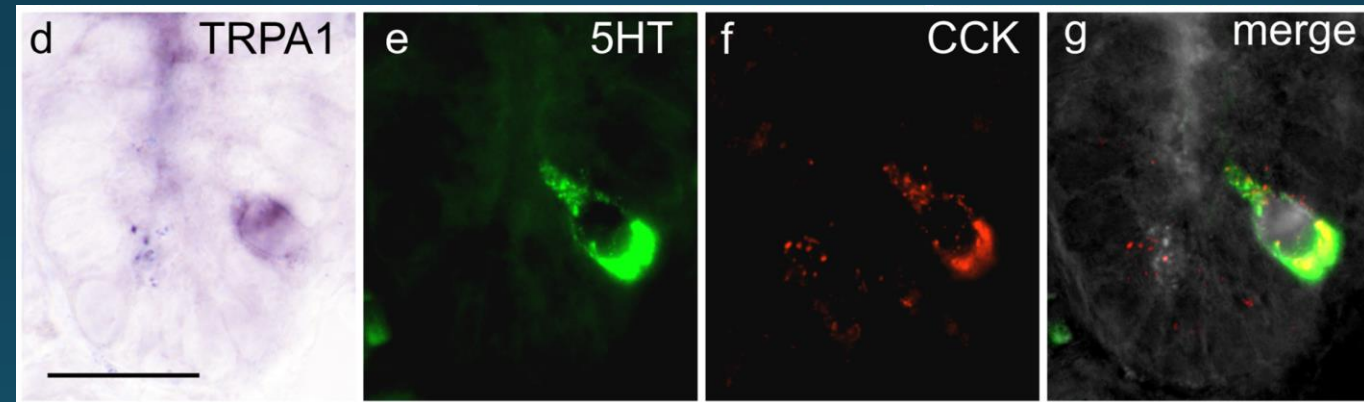


Slide courtesy of D. Bravo

Host-mediated effects of phytonutrients in production animals: pioneer research

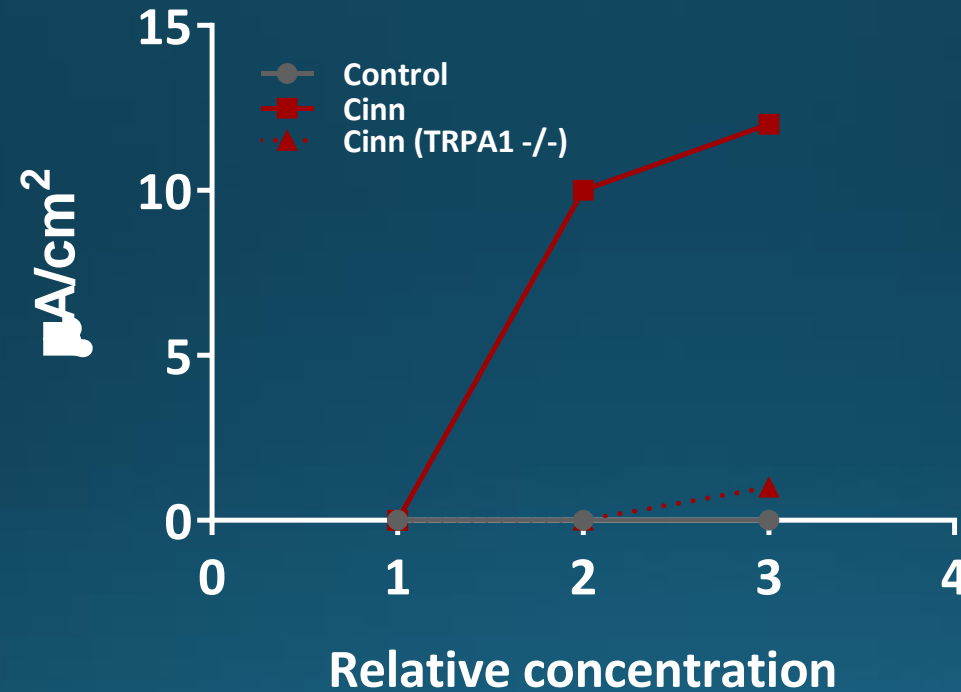


Transient receptor potential (TRP)A₁ is expressed in enteroendocrine cells of the duodenum



Co-expression with CCK: possible mechanism for digestive effects of cinnamon and garlic?

Host-mediated effects of phytonutrients in production animals: pioneer research



Cinnamaldehyde increases nutrient flux in the duodenum via TRPA1



Host-mediated effects of phytonutrients in production animals: pioneer research



J. Dairy Sci. 96:1–14
<http://dx.doi.org/10.3168/jds.2013-7089>
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Immune and production responses of dairy cows to postruminal supplementation with phytonutrients

J. Oh,* A. N. Hristov,*¹ C. Lee,* T. Cassidy,* K. Heyler,* G. A. Varga,* J. Pate,* S. Walusimbi,* E. Brzezicka,* K. Toyokawa,* J. Werner,† S. S. Donkin,‡ R. Elias,§ S. Dowd,# and D. Bravoll

*Department of Animal Science, and

Phytonutrients as additives in ruminants: the unexpected target organ

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¹The Pennsylvania State University, University Park, U.S.A.

ADSA-ASAS Joint Annual Meeting, July 2016



J. Dairy Sci. 100:5974–5983
<https://doi.org/10.3168/jds.2016-12341>
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Host-mediated effects of phytonutrients in ruminants: A review¹

J. Oh,* E. H. Wall,† D. M. Bravo,† and A. N. Hristov*²

*Department of Animal Science, The Pennsylvania State University, University Park 16802



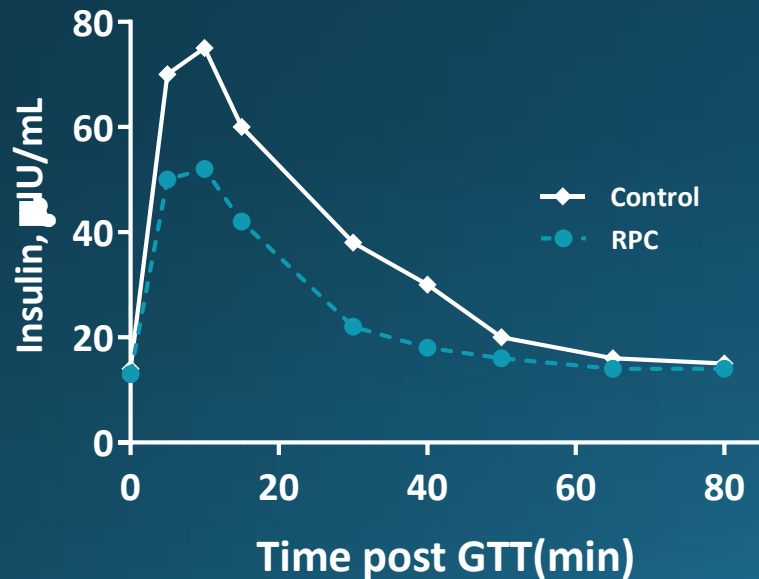
Host-mediated effects of phytonutrients in production animals: pioneer research



J. Dairy Sci. 100:1–14
<https://doi.org/10.3168/jds.2016-11665>
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Effects of rumen-protected *Capsicum* oleoresin on productivity and responses to a glucose tolerance test in lactating dairy cows

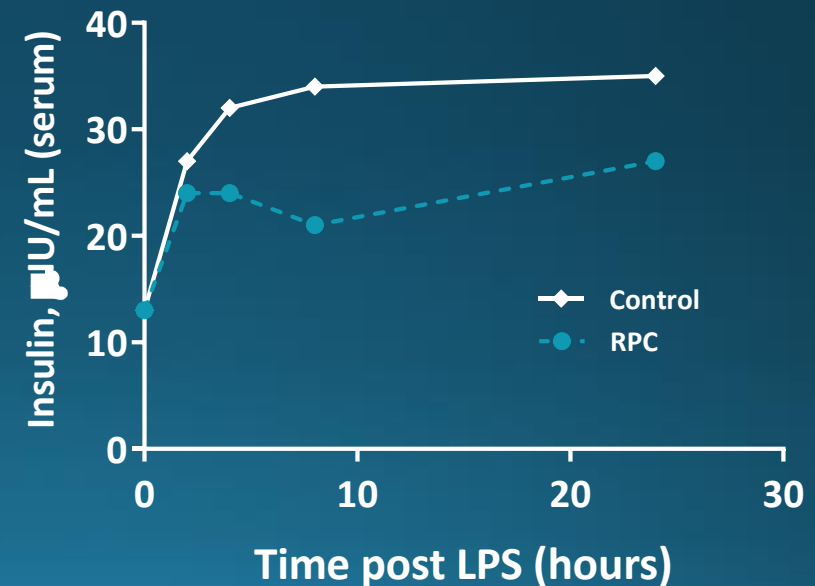
J. Oh,* M. Harper,* F. Giallongo,* D. M. Bravo,† E. H. Wall,† and A. N. Hristov*¹
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J. Dairy Sci. 100:1–12
<https://doi.org/10.3168/jds.2016-11666>
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Effects of rumen-protected *Capsicum* oleoresin on immune responses in dairy cows intravenously challenged with lipopolysaccharide

J. Oh,* M. Harper,* F. Giallongo,* D. M. Bravo,† E. H. Wall,† and A. N. Hristov*¹
*Department of Animal Science, The Pennsylvania State University, University Park 16802



Host-mediated effects of phytonutrients in production animals: pioneer research

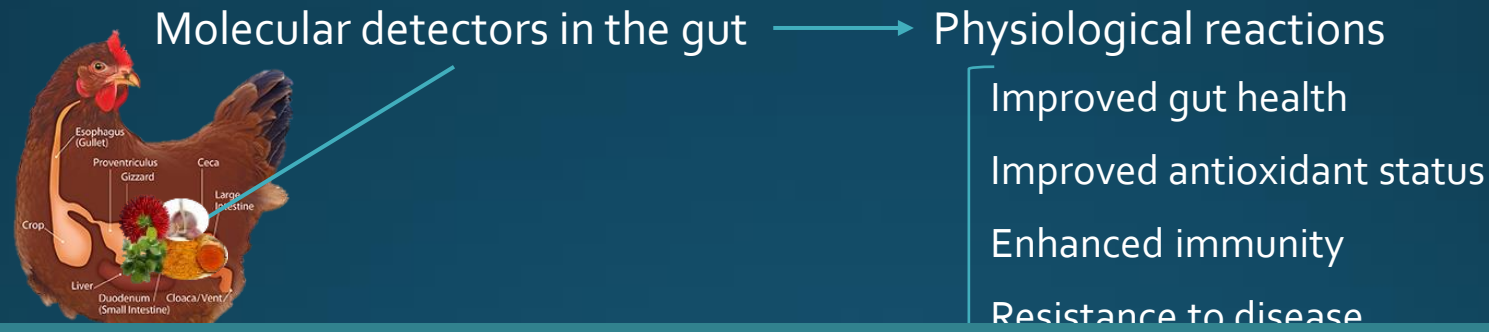


537 Effects of rumen-protected capsicum alone or in a combination with an artificial sweetener on productivity and fat mobilization in early lactation dairy cows. J. Oh¹, M. T. Harper¹, A. Melgar*¹, S. Räisänen¹, X. Chen^{1,2}, K. Nedelkov^{1,3}, E. H. Wall⁴, and A. N. Hristov¹, ¹*The Pennsylvania State University, University Park,*

In this experiment, dietary supplementation of RPC, but not artificial sweetener, appeared to increase milk production and feed efficiency in dairy cows following feed restriction to induce sub-clinical ketosis and

Second generation phytonutrients in animal production

- Important discoveries revealed that phytonutrients elicit host-mediated effects in production animals



Most of the Scientific community today works under this paradigm.

Improved economic growth efficiency

- Observed across species
- Phytonutrients detected by gut sensing machinery
- Molecular reactions lead to systemic responses
- Clear opportunity for next generation phytonutrients

Second generation phytonutrients in animal production

- And yet...
- Industry continues to work under the first-generation paradigm
- Virtually all phytonutrients are positioned as natural replacements for antibiotic growth promoters or antibiotics
 - Efficacy, ROI, application
- Oversimplified, silver-bullet approaches are expected
- Regulatory status continues as flavoring agents and concerns loom regarding classification as drugs, chemicals, or antimicrobials



How can we apply the knowledge & move forward?

ANIMAL NUTRITION



MEDICINE



Phytonutrients: the next generation

nature plants

Perspective | Published: 31 July 2017

Demystifying traditional herbal medicine with modern science

Fu-Shuang Li & Jing

Crit Rev Food Sci Nutr. 2018 Jul 3;58(10):1688-1705. doi: 10.1080/10408398.2017.1279121. Epub 2017 Jul 5.

The effects of food essential oils on cardiovascular diseases: A review.

Saljoughian S¹, Roohinejad S^{2,3}, Bekhit AEA⁴, Greiner R², Omidizadeh A¹, Nikmaram N⁵, Mousavi Khaneghah A⁶.

Article

TRPV1 Antagonists as Novel Anti-Diabetic Agents: Insulin

Planta Med. 2019 Feb;85(3):239-248. doi: 10.1055/a-0758-0188. Epub 2018 Oct 25.

Essential Oils as Treatment Strategy for Alzheimer's Disease: Current and Future

Curr Cancer Drug Targets. 2018;18(10):957-966. doi: 10.2174/15

Anticancer Properties of Essential Oils

Andrade MA¹, Braga MA², Cesar PHS², Trento MVC², Espo

Biomed Pharmacother. 2018 Aug;104:343-365. doi: 10.1016/j.biopha.2018.05.044. Epub 2018 May 25.

Phytochemistry and pharmacology of anti-depressant medicinal plants: A review

Martins J¹, S B².

Biotechnol Adv. 2018 Nov 1;36(6):1633-1648. doi: 10.1016/j.biotechadv.2018.03.014. Epub 2018 Mar 27.

Dietary nutraceuticals as backbone for bone health.

Pandey MK¹, Gupta SC², Karelia D³, Gilhooley PJ⁴, Shakibaei M⁵, Aggarwal BB⁶.

Neural Regen Res. 2019 Mar;14(3):441-445. doi: 10.4103/1673-5374.245467.

Essential oils and functional herbs for healthy aging.

Agatonovic-Kustrin S¹, Kustrin E², Morton DW³.

Int J Mol Sci. 2017 May 16;18(5). pii: E1068. doi: 10.3390/ijms18051068.

The Role of Phytochemicals in the Inflammatory Phase of Wound Healing. IL-6 Level in Depression Mice with Basil Leaf

Shah A¹, Amini-Nik S^{2,3,4}.

1.3889/oamjms.2019.819. eCollection 2019 Aug 30.

Centuri M¹, Hoshini L², Ghasemi FWA³, Ditarone L⁴

Phytonutrients: the next generation

- What do we need to get there?
 - Resist the tempting cause-and-effect trap
 - Acknowledge host-mediated responses
 - Work on regulatory classification and positioning
 - Educate the industry
 - Integrate and align the progress of science with industry understanding/use and regulatory frameworks! (alternative: death of the technology)
 - Actively explore next-generation concepts!

Phytonutrients: the next generation



Let's move together towards this paradigm!



Thank you.