Your Gut 2.0:
Unraveling
Oxalate Intolerance

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Wise Traditions Conference
October 20, 2023

DISCLAIMER

This presentation is provided for educational and informational purposes only and does not constitute providing medical advice or professional services.

The information provided should not be used for diagnosing or treating a health problem or disease, and those seeking personal medical advice should consult with a licensed physician or healthcare provider.

Setting the Stage

Magnesium in Drinking Water

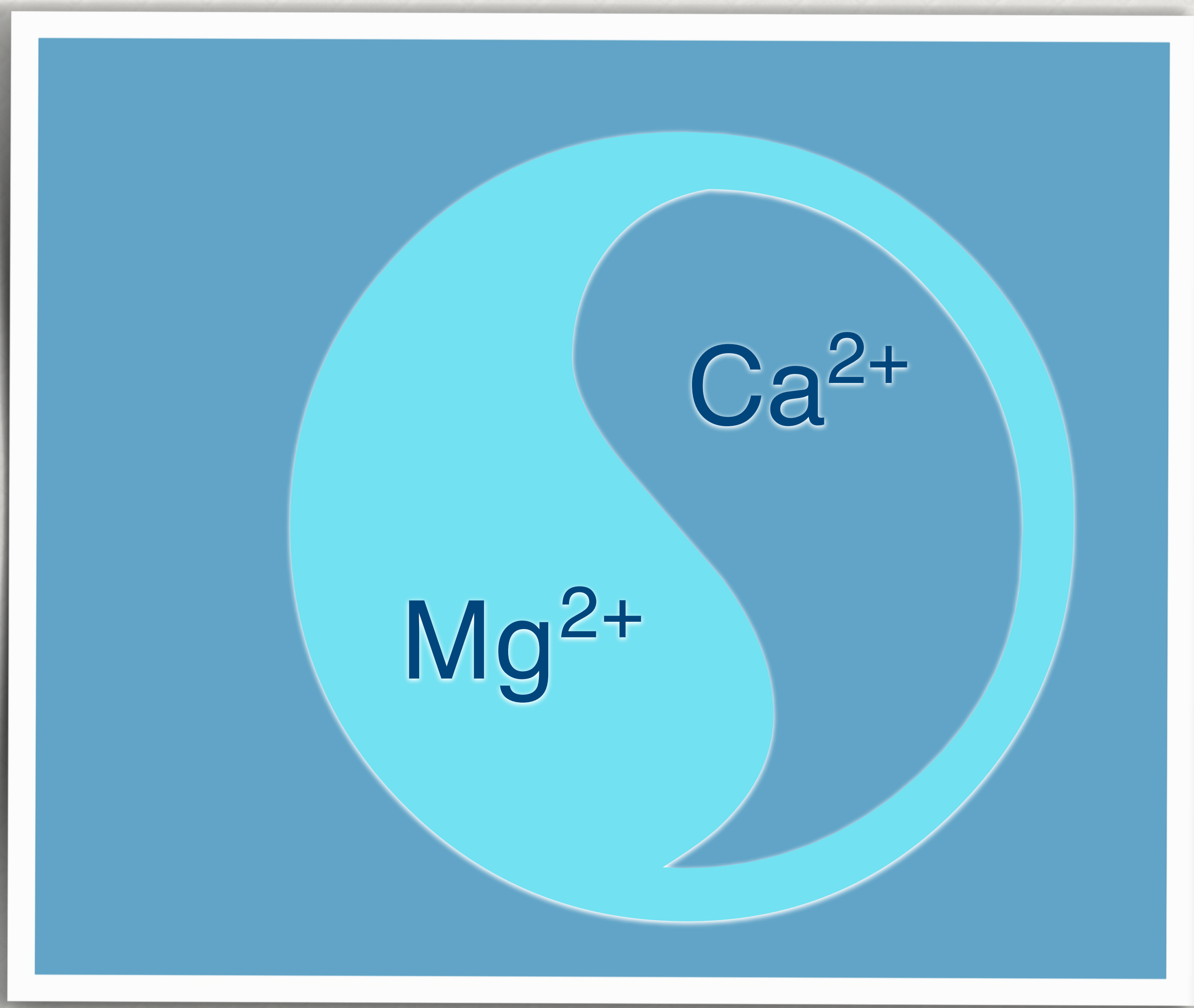
High Magnesium =

> 25 mg/L Mg^{2+}

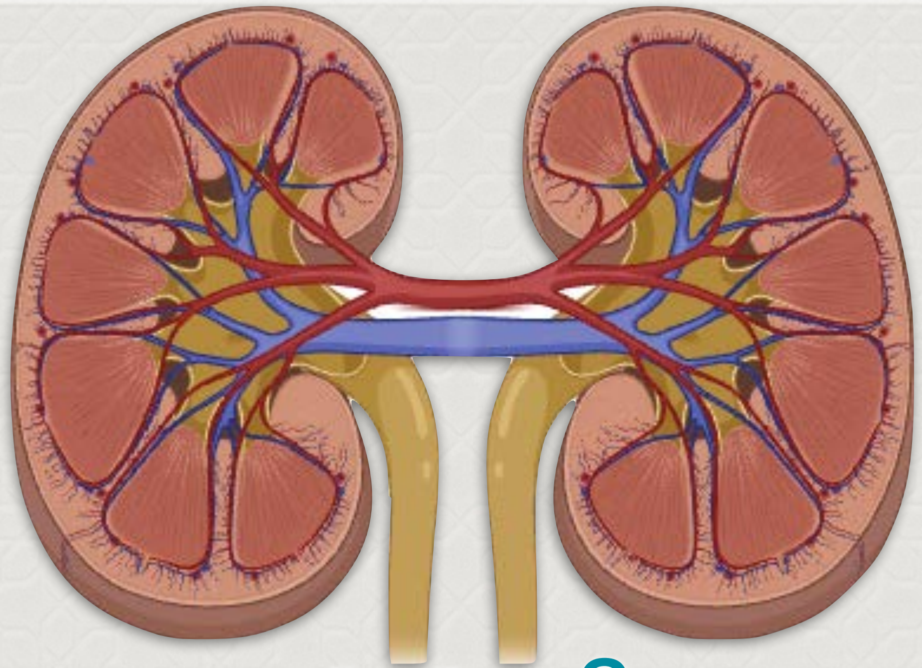
= Heart Healthy

Magnesium Missing in Drinking Water - A Persistent Link to Cardiovascular Disease?; Foster, R., 2020

Major Minerals



Magnesium: The Forgotten Electrolyte—A Review on Hypomagnesemia; Ahmed, F., & Mohammed, A., 2019



Mg^{2+}

Kidneys play a major role in Mg^{2+} homeostasis

Mg^{2+} inhibits calcification

Mg^{2+} deficiency is linked to the progression of CKD and other chronic diseases

The emerging role of magnesium in CKD; Sakakguchi, Y., 2022

Kidney Stone Disease alternative terms:

Nephrolithiasis = nephro (kidney) + lithias (stone)

Urolithiasis = uro (urinary) + lithias (stone)

Urinary Stones - as old as time

Bladder stones more prevalent in earlier civilizations

Kidney stones notable increase in the last 100 years

- 4-fold surge in last 50 years
- 80% are CaOx

Global prevalence range - 5% to 20%

- Rising in women and children
    - Pediatric increase 5-fold in last decade

Recurrence rate 50% in 5 years for adult

History, epidemiology and regional diversities of urolithiasis; López, M., & Hoppe, B., 2010
Kidney stone prevention; Peerapen, P. & Thongboonkerd, V., 2023

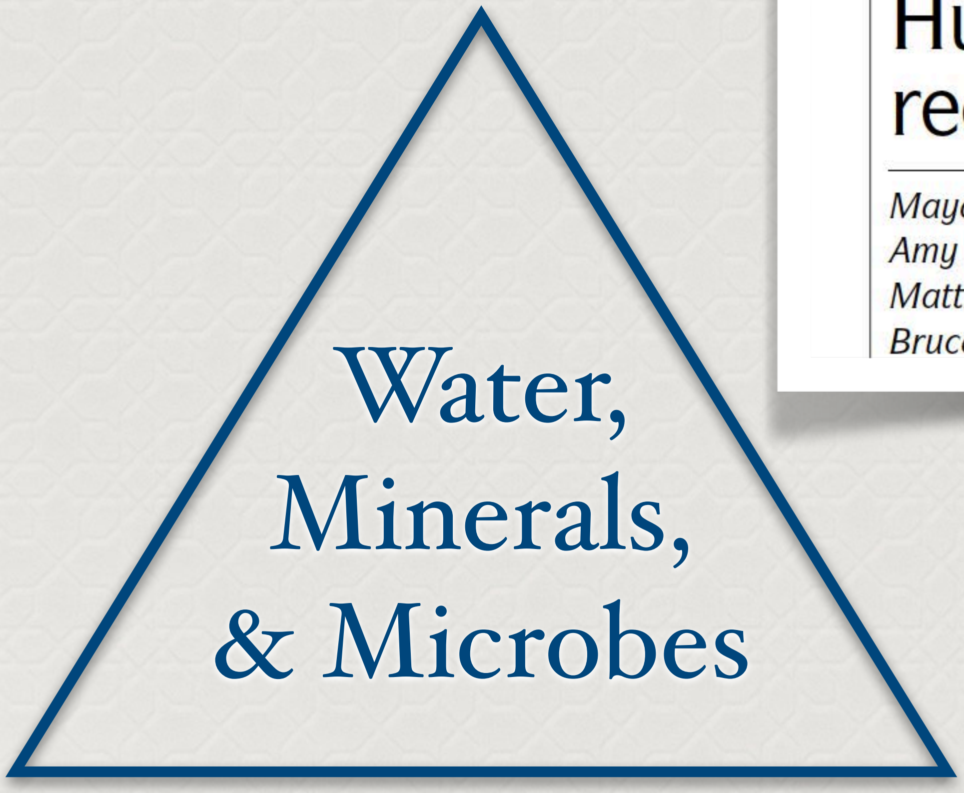

2021

REVIEWS

Check for updates

Human kidney stones: a natural record of universal biomineralization

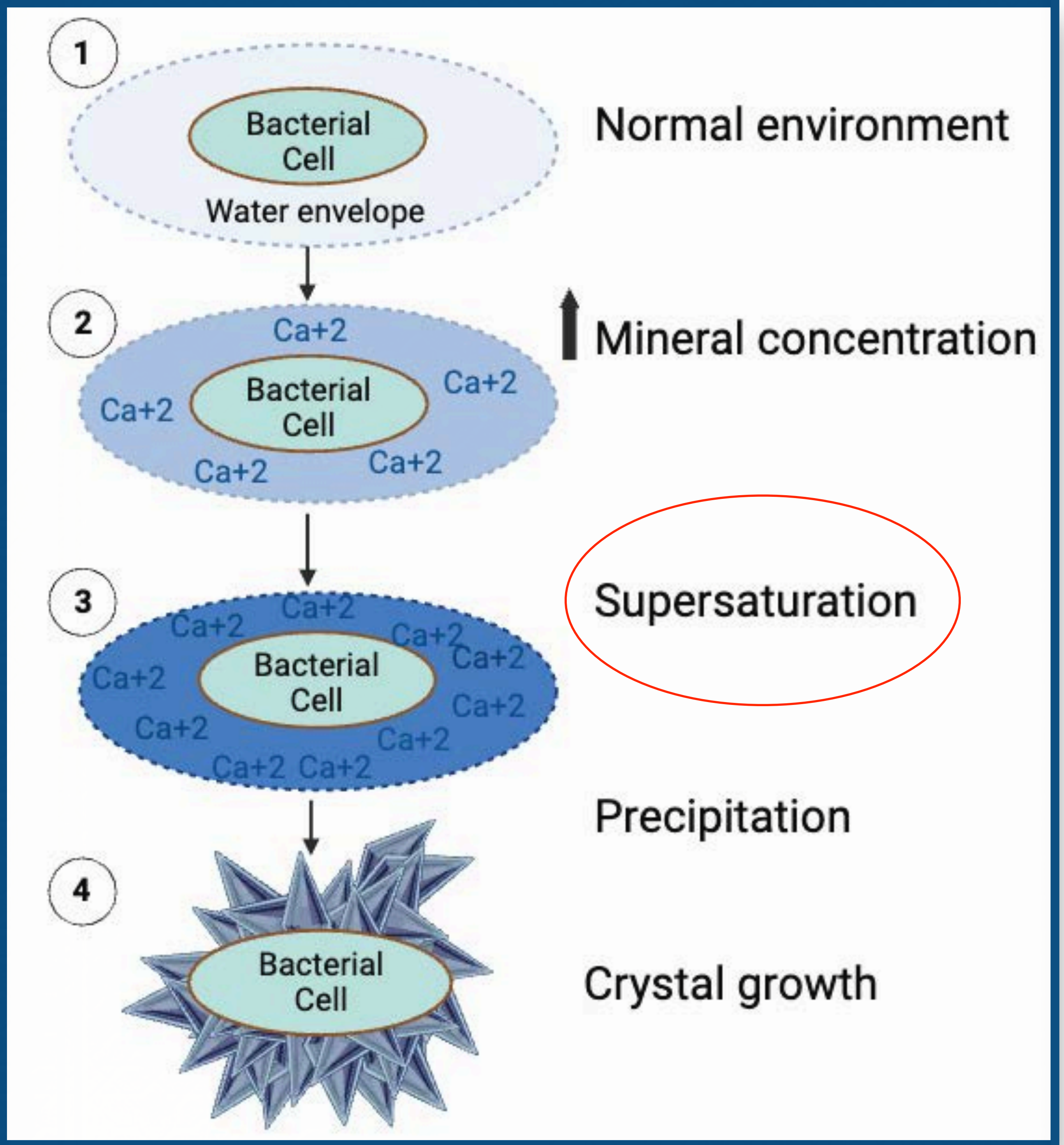
Mayandi Sivaguru[1,2]✉, Jessica J. Saw[1,3,4], Elena M. Wilson[1,5], John C. Lieske[6,7], Amy E. Krambeck[8,9], James C. Williams[10], Michael F. Romero[6,11], Kyle W. Fouke[12], Matthew W. Curtis[13], Jamie L. Kear-Scott[13], Nicholas Chia[10,14] and Bruce W. Fouke[1,2,5,15,16,17]✉



Bio-mineralization

Human kidney stones: a natural record of universal biomineralization; Sivaguru, M., et al., 2021

Bacteria Create Fossils



Bio-mineralization

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2021

Original Investigation

Kidney360

In Vivo Entombment of Bacteria and Fungi during Calcium Oxalate, Brushite, and Struvite Urolithiasis

Jessica J. Saw,[1,2,3] Mayandi Sivaguru,[1] Elena M. Wilson,[1,4] Yiran Dong,[1] Robert A. Sanford,[1,5] Chris J. Fields,[6] Melissa A. Cregger,[1,7] Annette C. Merkel,[1,4] William J. Bruce,[1,4] Joseph R. Weber,[1,4] John C. Lieske,[8,9] Amy E. Krambeck,[10,11] Marcelino E. Rivera,[11] Timothy Large,[11] Dirk Lange,[12] Ananda S. Bhattacharjee,[1] Michael F. Romero,[13,14] Nicholas Chia,[9,10] and Bruce W. Fouke[1,4,5,6,15]

Kidney stones similar to other bio-mineralization forms - in natural and manmade environments.

All forms are significantly influenced by microorganisms (microbiome).

Kidney Stone Disease

> 80% of stones composed of
Calcium Oxalate crystals

97.2% of stones contain Bacteria
70% are multi-antibiotic resistant

Linked to several systemic disorders -

CVD

Diabetes

Obesity

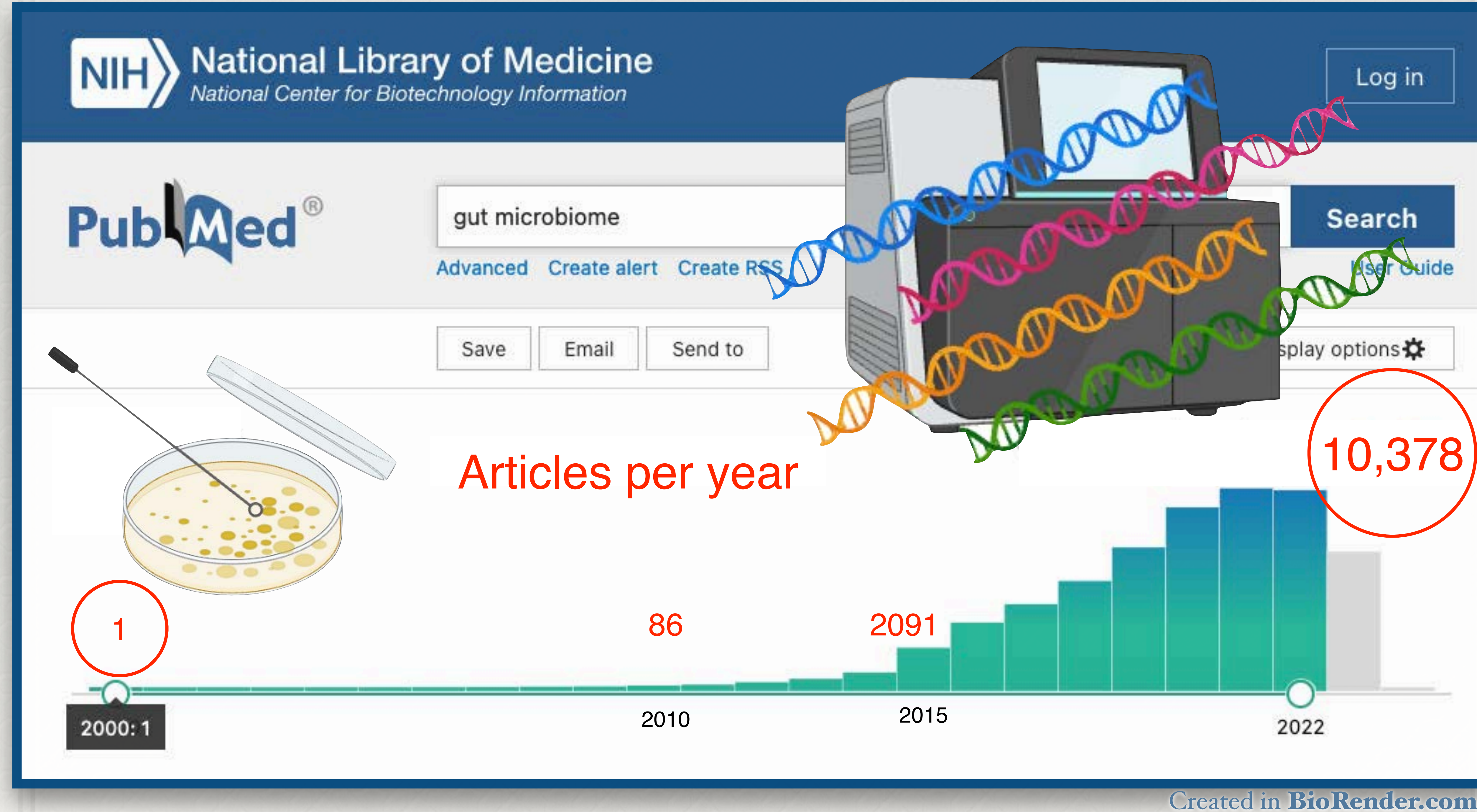
MetS

IBD

Crohn's

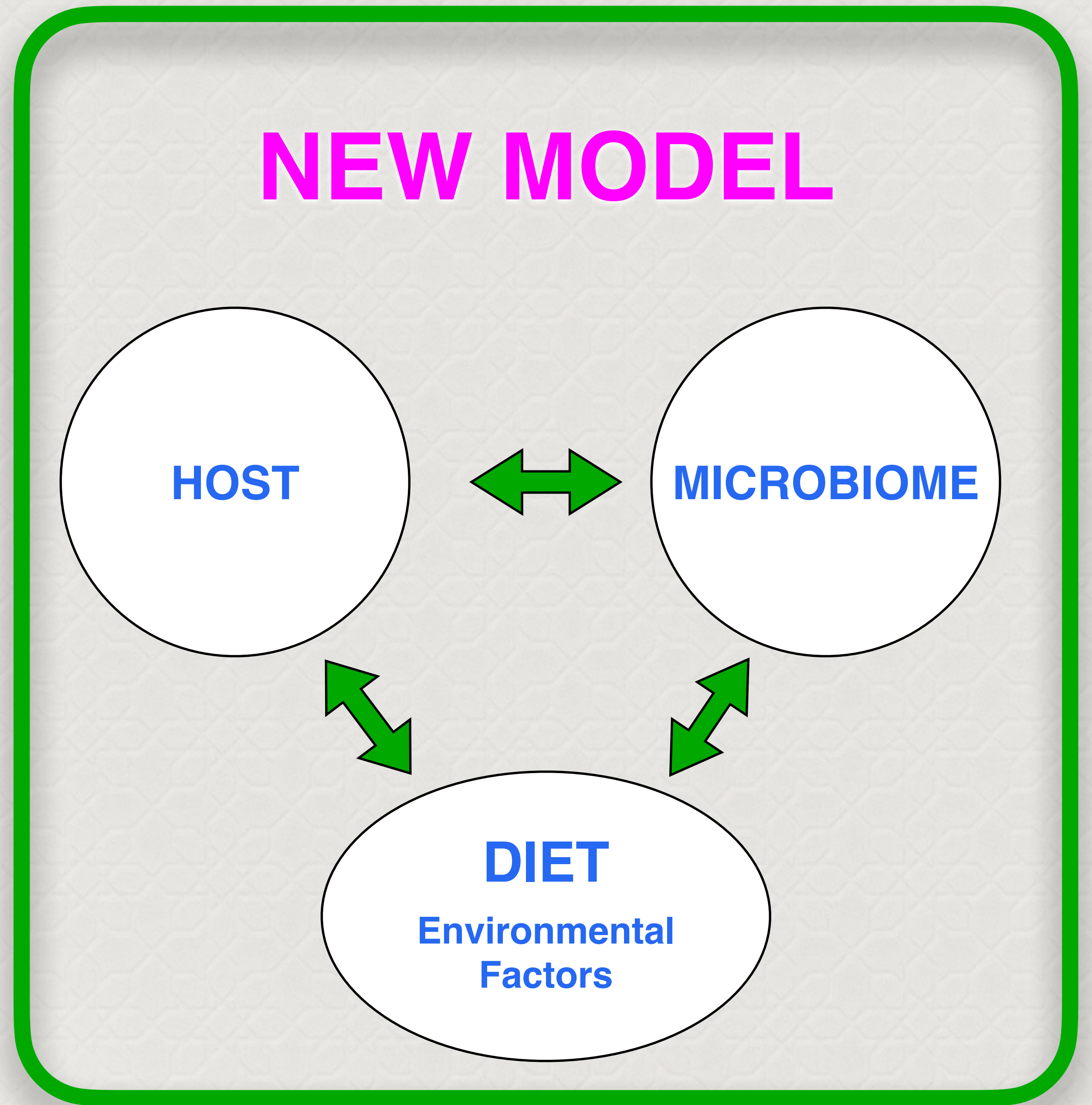
Recent advances on the mechanisms of kidney stone formation (Review); Wang, Z., et al., 2021
The Use of Antibiotics and Risk of Kidney Stones; Joshi, S., & Goldfarb, D., 2019

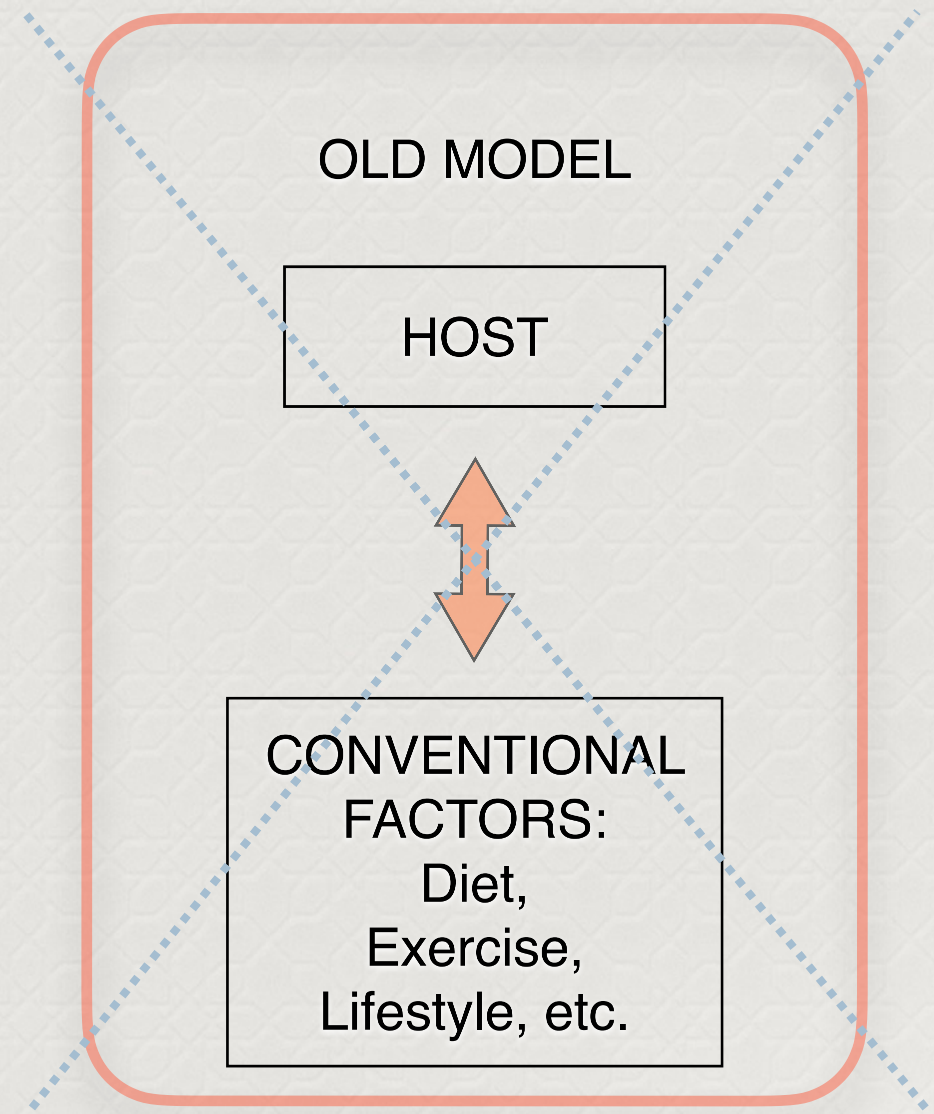
Search “gut microbiome”



Next-Generation Technology

https://pubmed.ncbi.nlm.nih.gov/?term=gut+microbiome&filter=years.2000-2022&timeline=expanded

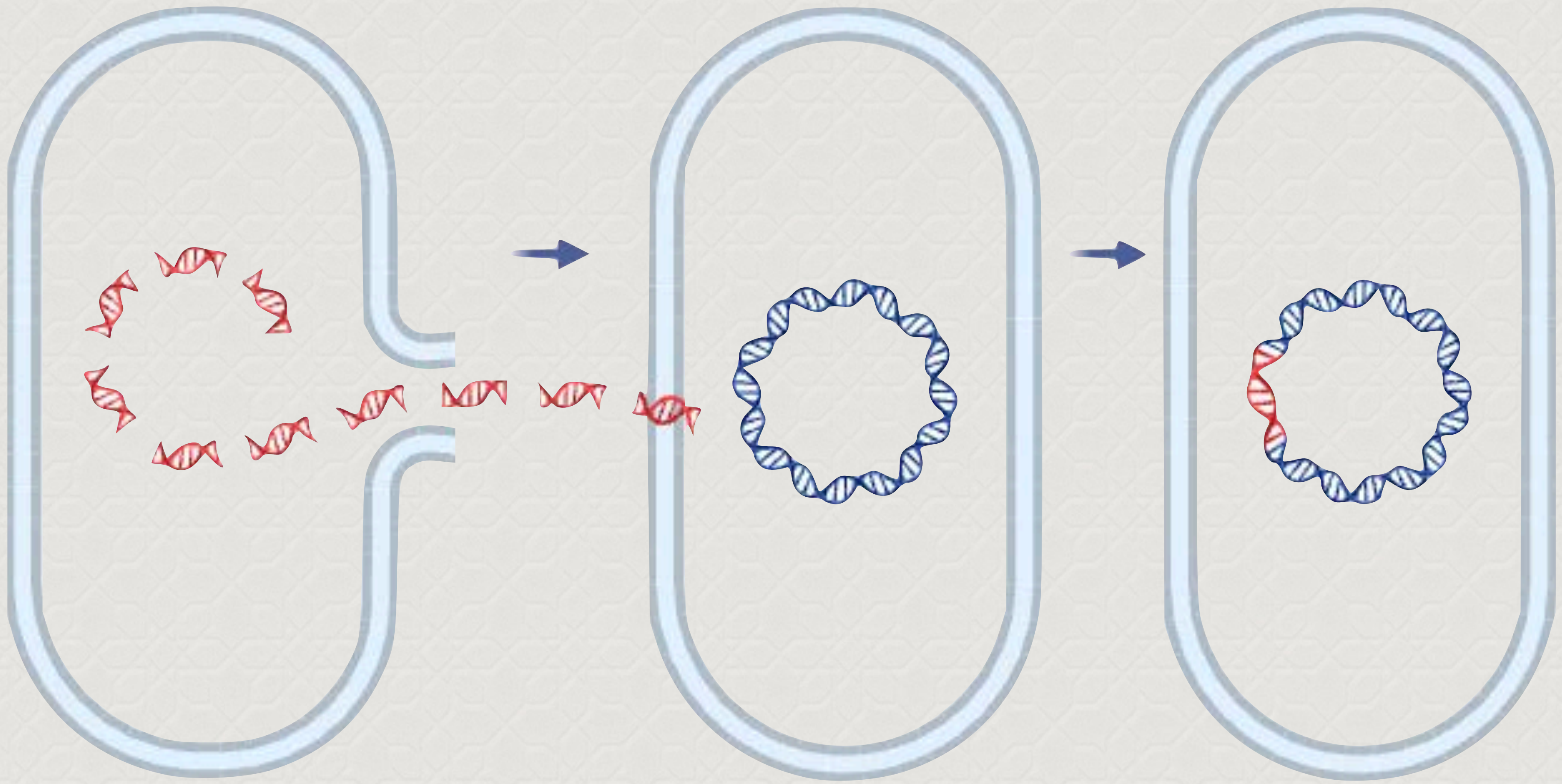




HOLOBIONT

"Whole Unit of Life"

Bacteria Adapt Quickly



150x more genetic content than human

- Greater ability to survive critical environmental changes
- Radically faster than human genetic evolution

Aging, frailty, and the microbiome—how dysbiosis influences human aging and disease.
Haran, J., & McCormick, B., 2021

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nature

2014

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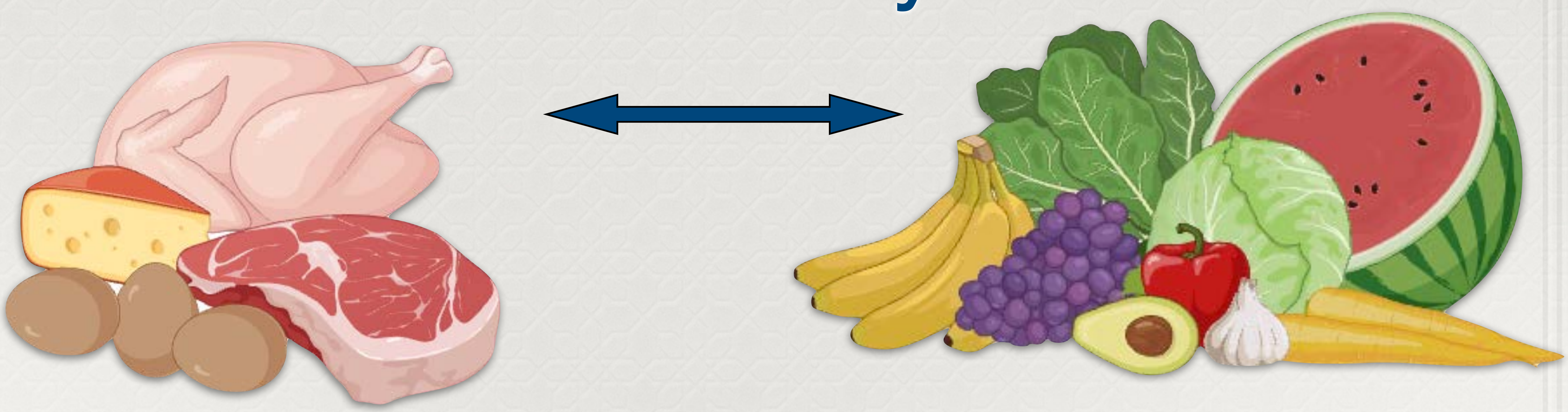
nature › letters › article

Published: 11 December 2013

Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David, Corinne F. Maurice, Rachel N. Carmody, David B. Gootenberg, Julie E. Button, Benjamin E. Wolfe, Alisha V. Ling, A. Sloan Devlin, Yug Varma, Michael A. Fischbach, Sudha B. Biddinger, Rachel J. Dutton & Peter J. Turnbaugh

2 to 5 days



Diet rapidly and reproducibly alters human gut microbiome. David, L., et al., 2014

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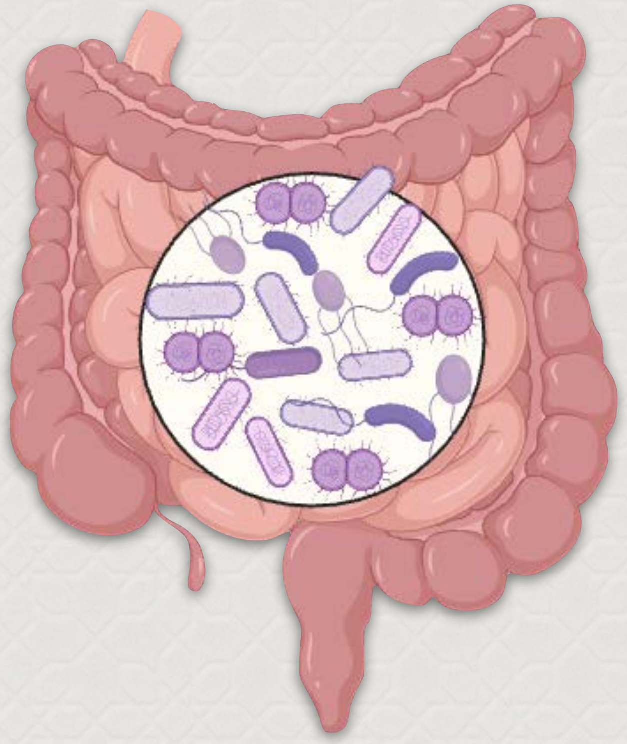
Bacterial Metabolites

~ 30% of blood metabolites are produced by gut microbes

- SCFAs
- Hormones
- Vitamins



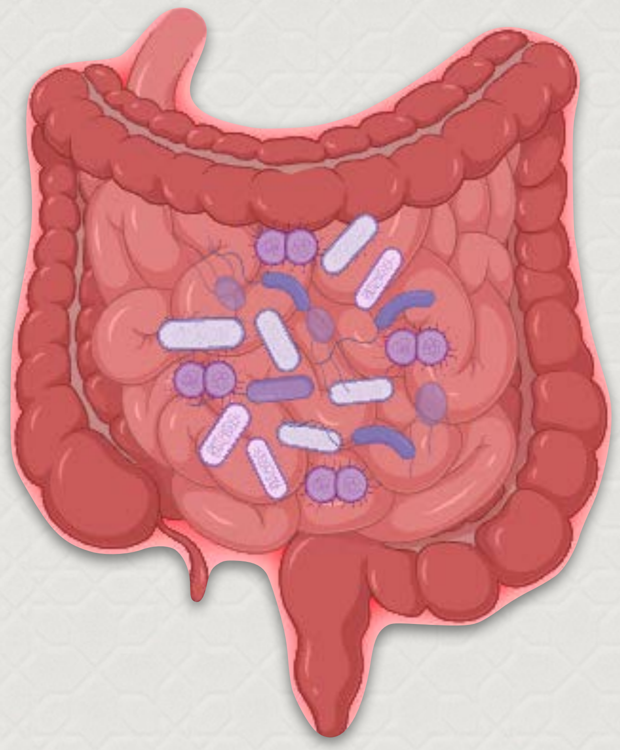
Microbiota produce, modify, and influence vitamin absorption

“Pantryome” concept - bacteria can take, donate, or share metabolites with other bacteria - crosstalk

Bidirectional micronutrient - microbiome axis

Vitamins as regulators of calcium-containing kidney stones—new perspectives on the role of the gut microbiome.
Chmiel, J., et al., 2023

Dysbiosis = Losing Diversity



Gain of function -
acquired microbial functions that cause disease

Loss of function -
loss of microbes and their beneficial functions

Difficult to detect due to lack of growth pattern

KSD is a good example of loss of function

Loss of function dysbiosis associated with antibiotics and high fat, high sugar diet. Miller, A., et al., 2019

Dysbiosis

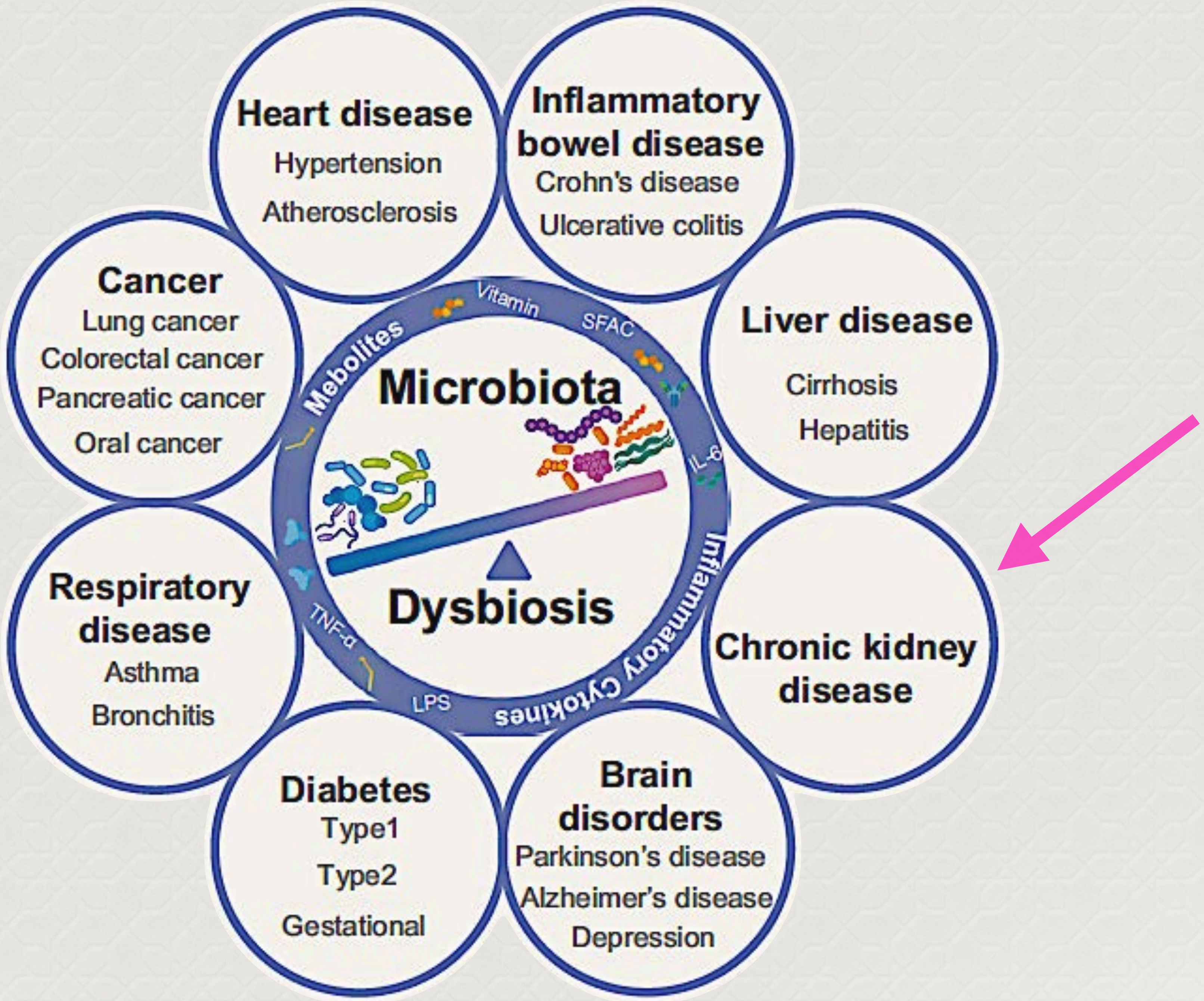


Fig. 4 Human microbiota dysbiosis contributes to various diseases

Microbiota in health and diseases. Hou, K., et al., 2022

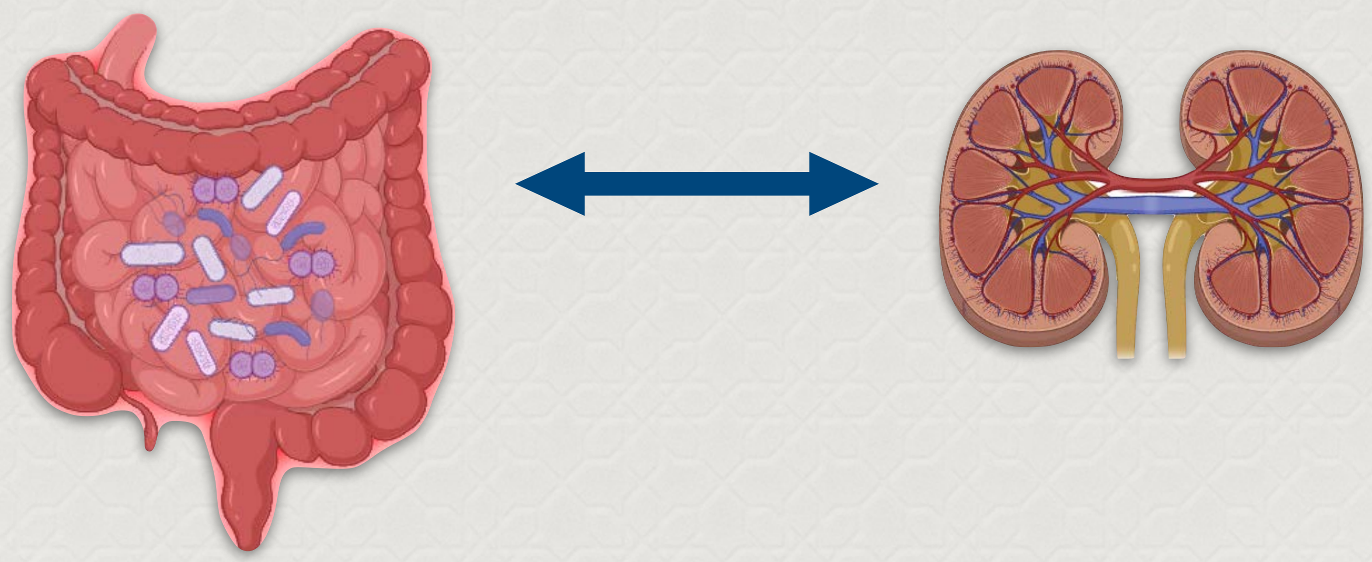
Gut - Kidney Axis

Humans lack enzymes to degrade oxalate

Over-accumulation of oxalate leads to toxicity

KSD is the most common form of oxalate toxicity

Microbes can degrade oxalate through multiple pathways



KSD provides a direct link between the gut and disease

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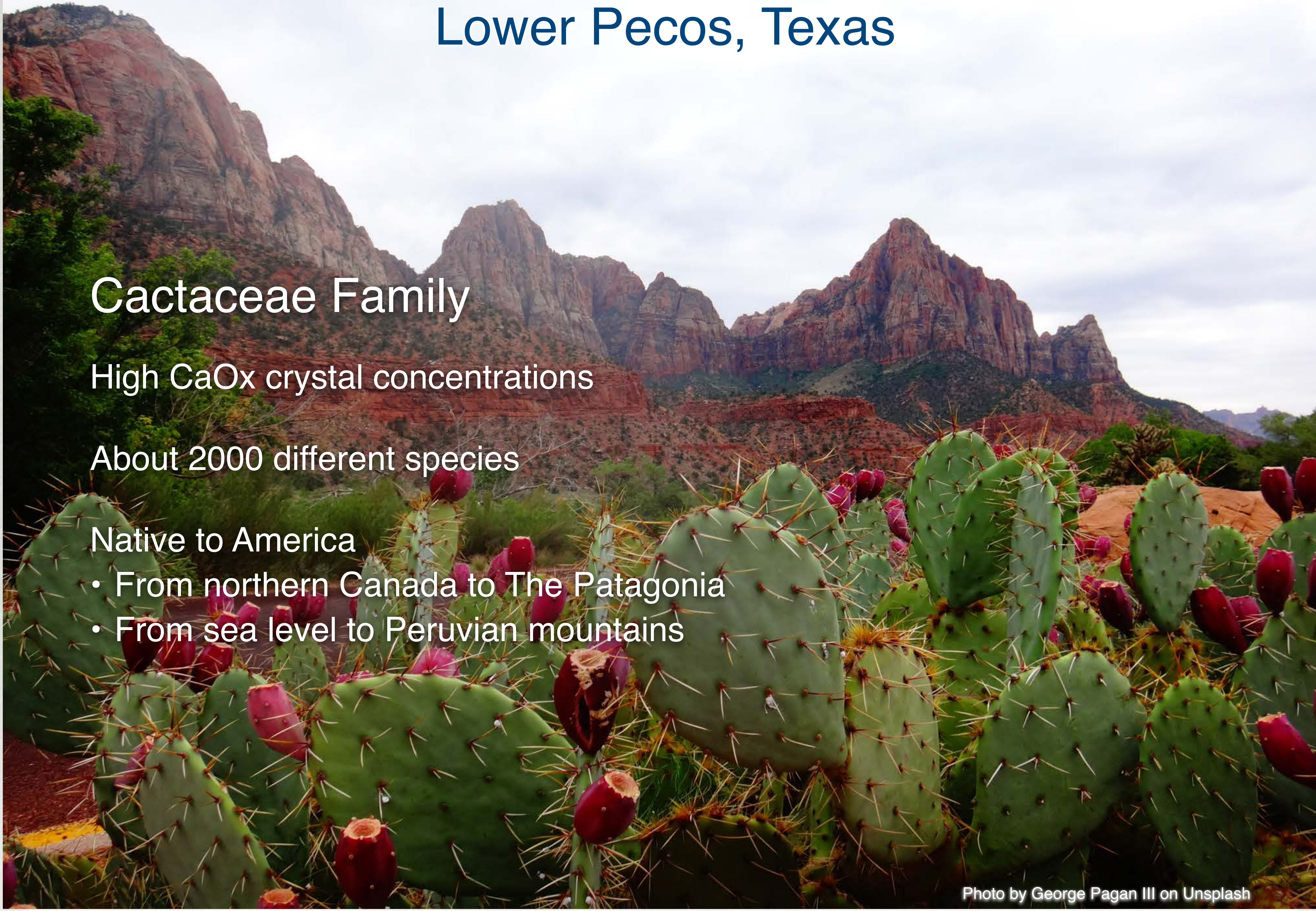
Loss of function dysbiosis associated with antibiotics and high fat, high sugar diet. Miller, A., et al., 2019

Ancestral Oxalate Consumption?

Lower Pecos, Texas



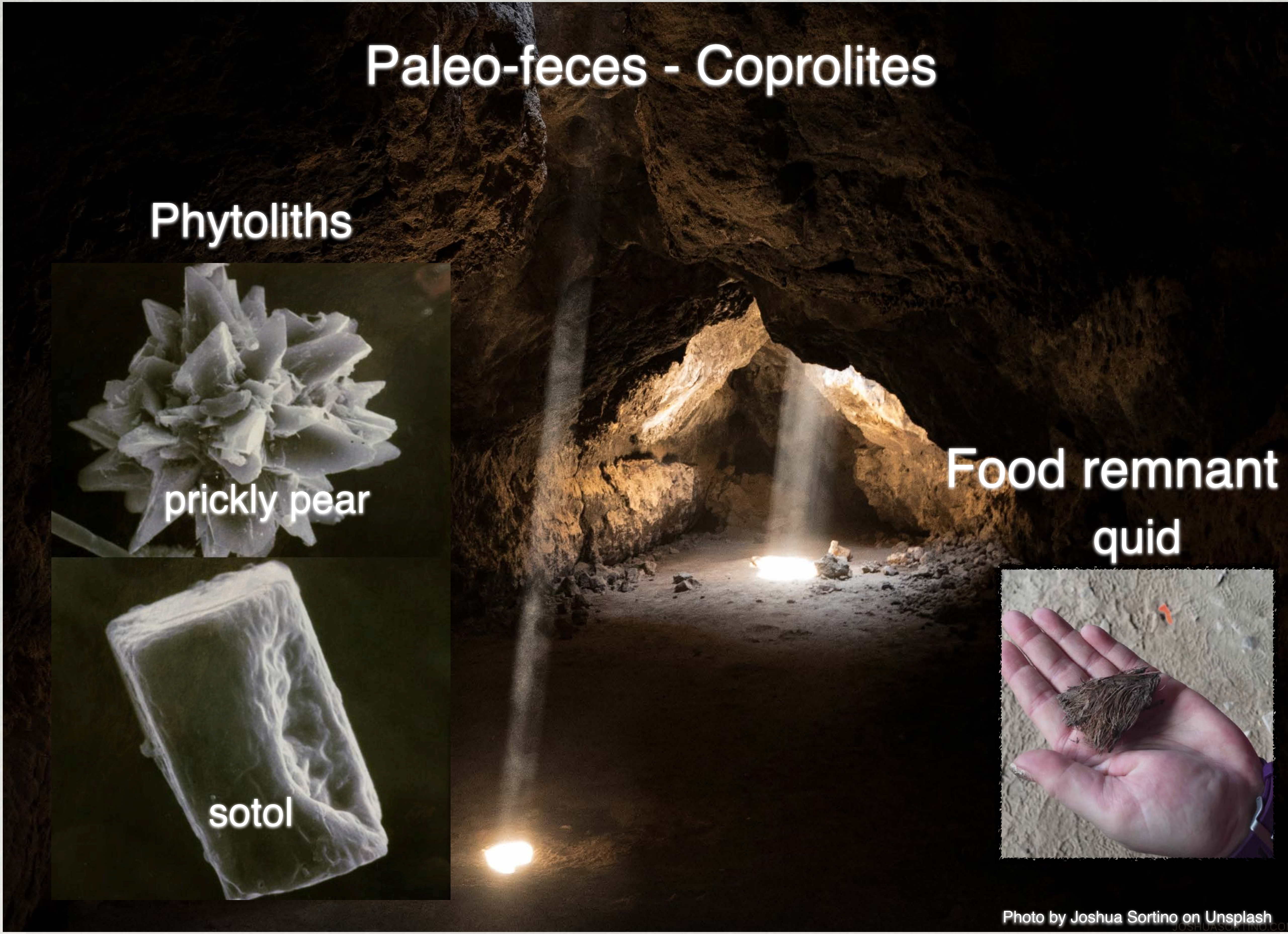
Cactaceae Family

High CaOx crystal concentrations

About 2000 different species

Native to America
- From northern Canada to The Patagonia
- From sea level to Peruvian mountains

Photo by George Pagan III on Unsplash



Pervasiveness of Phytoliths in Prehistoric Southwestern Diet … Dental Microwear. Reinhard, K., & Danielson, D., 2005

Mescalero Apache Women

Roasting Agave Hearts, 1900

Ethnohistoric records of Hunter-gatherer diet Lower Pecos, Riley, T., 2018

The Induction of Oxalate Metabolism In Vivo Is More Effective with Functional Microbial Communities… Miller, A., et al., 2017

Inuits Eat Plants - High Oxalate

> 1000 edible plant species

Freezing
Dehydration
Slow-cooking
Baking, steaming, boiling
Oil-pack
Fermenting

"Eskimo ice cream"

Greens, berries, and roots

Wild celery

Tall cottongrass

Lichen and moss

Algae, kelp, seaweed

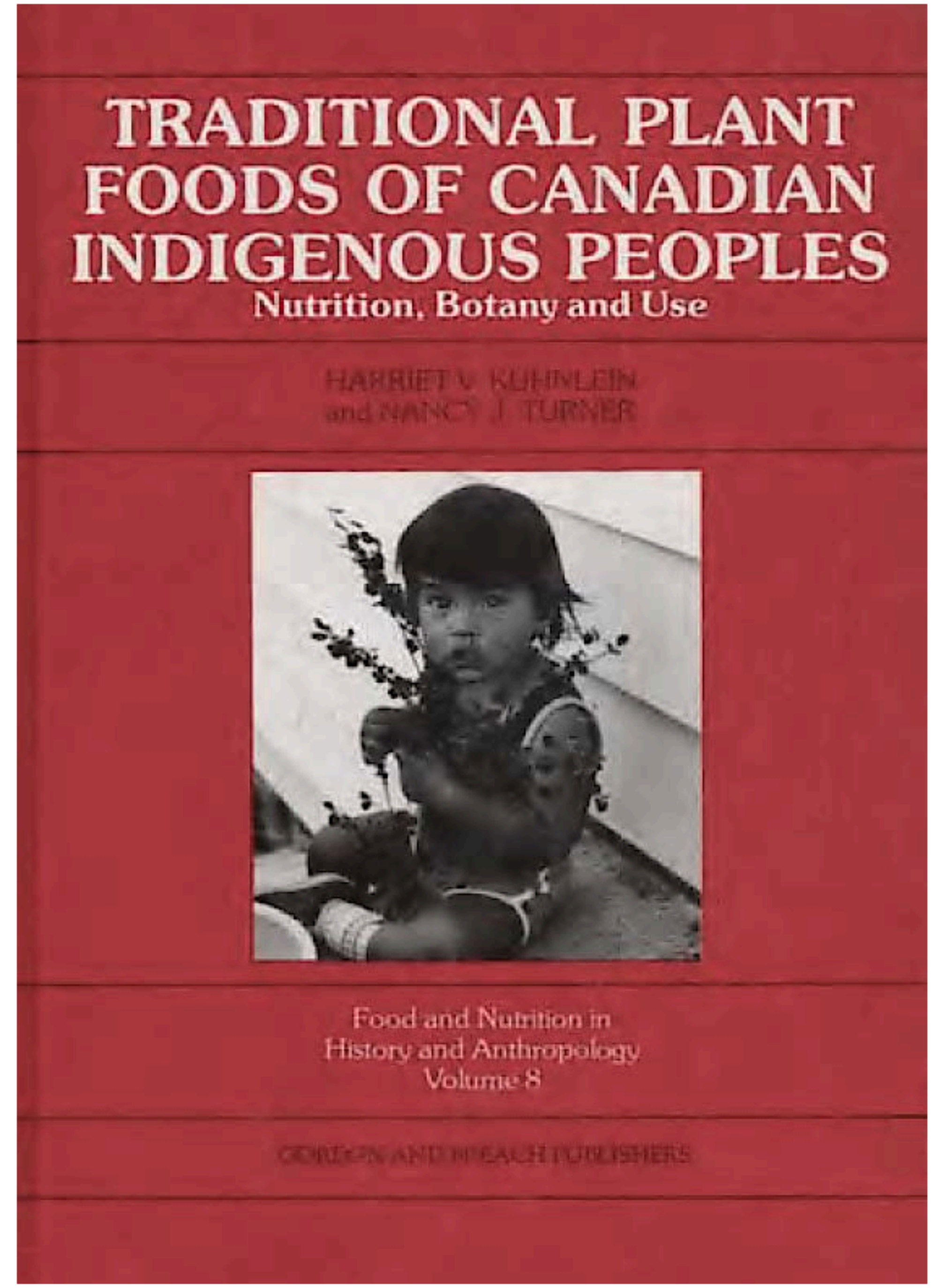


Photo by Jesse Brack on Unsplash

Traditional plant foods of Canadian indigenous peoples: nutrition, botany and use. Kuhlein, H., & Turner, N., 1991

Africans Eat Plants - High Oxalate

- Cassava
- Sweet potato
- Cowpea
- Pigweed
- Pumpkin
- African cabbage
- Malabar spinach
- Nightshade berries

Oxalate Levels in Selected African Indigenous Vegetable Recipes… Wakhanu, J., et al., 2015

Mediterranean Wild Vegetables

The Mediterranean basin is characterized by an enormous biodiversity and a rich heritage of edible wild plants, which since Ancient times have represented an important source of nutrients for rural communities, both for food and medicinal uses.

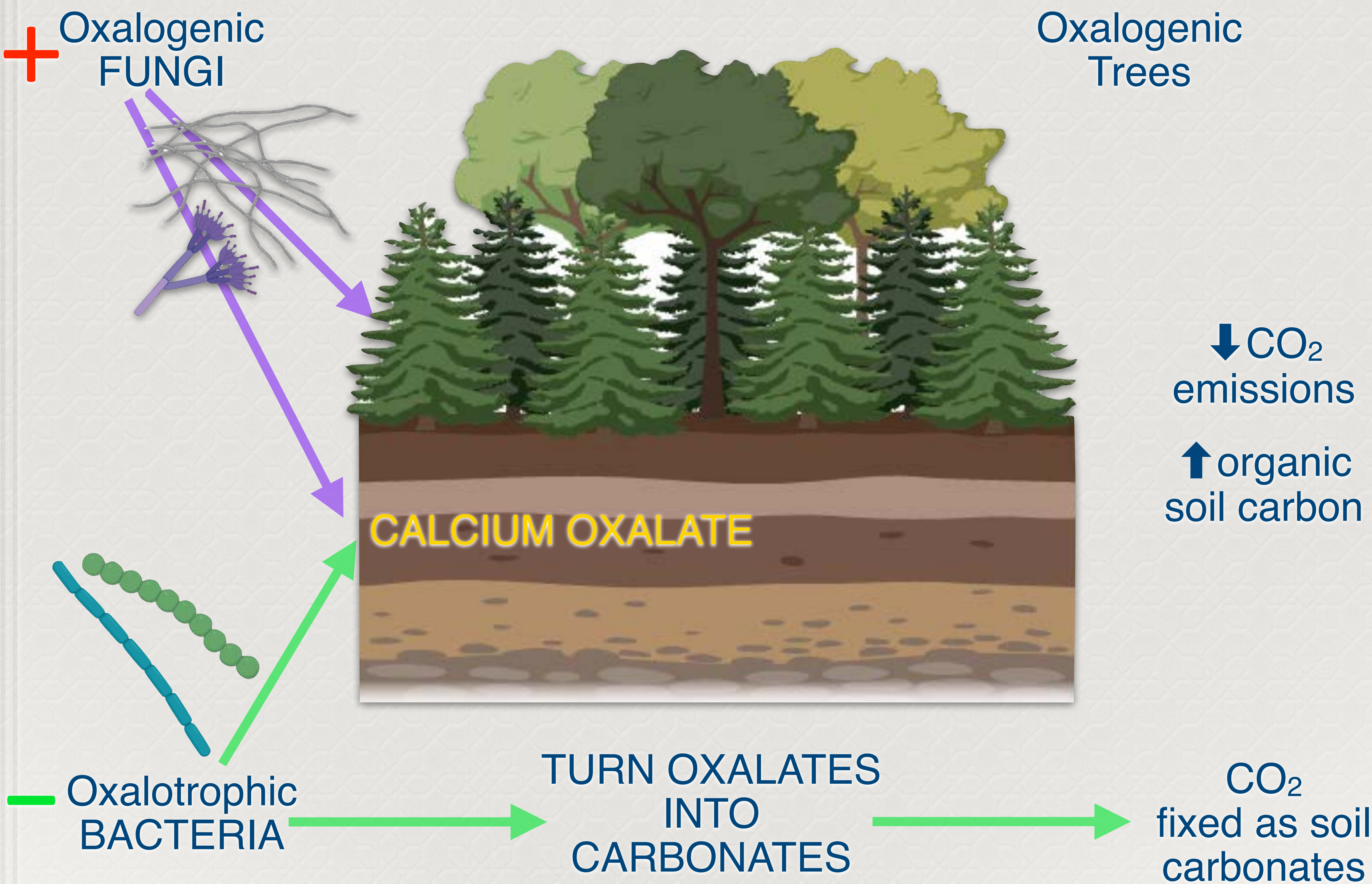
… Oxalic acid was the most relevant organic acid found in the analyzed samples, due to its role as an antinutrient.

… The boiling process can reduce the amount of the antinutrient oxalic acid in wild greens.

Nutritional and Phytochemical Composition of Mediterranean Wild Vegetables after Culinary Treatment. García-Herrera, P., et al., 2020

Oxalate Foe or Friend?

Oxalates in Nature



Oxalate Carbonate Pathway—Conversion and Fixation of Soil Carbon… Syed, S., et al., 2020

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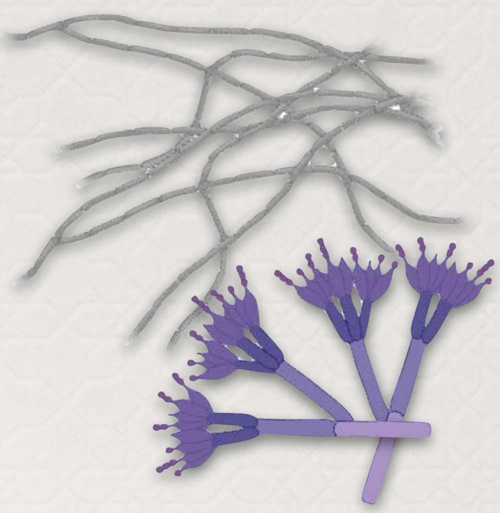
2014

Fungal Biology Reviews
Volume 28, Issues 2–3, October 2014, Pages 36-55

Review

Oxalate production by fungi: significance in geomycology, biodeterioration and bioremediation

Geoffrey Michael Gadd [a b], Jaleh Bahri-Esfahani [a c], Qianwei Li [a], Young Joon Rhee [a], Zhan Wei [a], Marina Fomina [a d], Xinjin Liang [a]



Fungi produce Oxalic acid

Bacteria consume Oxalate

Oxalate is the most oxidized carbon compound after CO_2

Oxalate production by fungi: significance in geomyycology… Gadd, G., et al., 2014

2012

ENVIRONMENTAL MICROBIOLOGY

Applied Microbiology International

Research Article

Fungi, bacteria and soil pH: the oxalate–carbonate pathway as a model for metabolic interaction

Gaëtan Martin, Matteo Guggiari, Daniel Bravo, Jakob Zopfi, Guillaume Cailleau, Michel Aragno, Daniel Job, Eric Verrecchia, Pilar Junier

Bacteria and fungi
Shape biological life above and below ground

Bacteria Degrade
⬆ pH

Bacteria alone
convert
strong acid (Oxalate)
to weaker one

Fungi Produce
⬇ pH

Oxalate increases
micronutrient
availability for plant uptake

Fungi, bacteria and soil pH: the oxalate–carbonate pathway as a model for metabolic interaction. Martin, G., et al., 2012

Oxalate function in humans?

HHS Public Access
Author manuscript
Nat Rev Nephrol. Author manuscript; available in PMC 2023 June 19.

Published in final edited form as:
Nat Rev Nephrol. 2023 February ; 19(2): 123–138. doi:10.1038/s41581-022-00643-3.

2023

Oxalate homeostasis

Theresa Ermer[1], **Lama Nazzal**[2], **Maria Clarissa Tio**[3], **Sushrut Waikar**[4], **Peter S. Aronson**[5], **Felix Knauf**[5,6,✉]

[1]Department of Surgery, Division of Thoracic Surgery, Yale School of Medicine, New Haven, CT, USA.

Three potential roles in human physiology

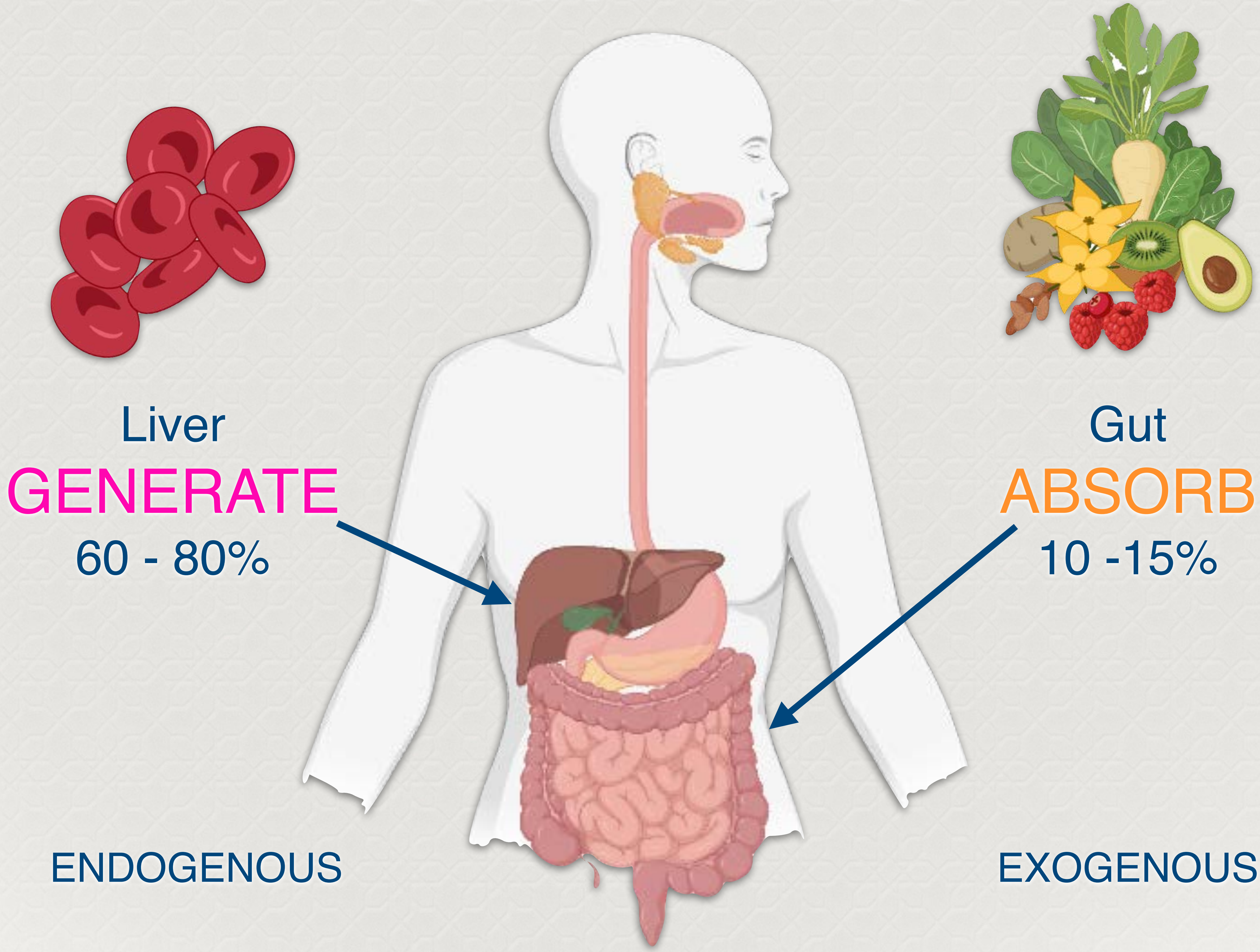
Stimulate the absorption of water, sodium, and chloride in kidney tubules

Assist in immune function to enhance phagocytosis through the production of H2O2

Contribute to RNA synthesis through formation of uracil and orotic acid

Oxalate Homeostasis. Ermer, T., et al., 2020

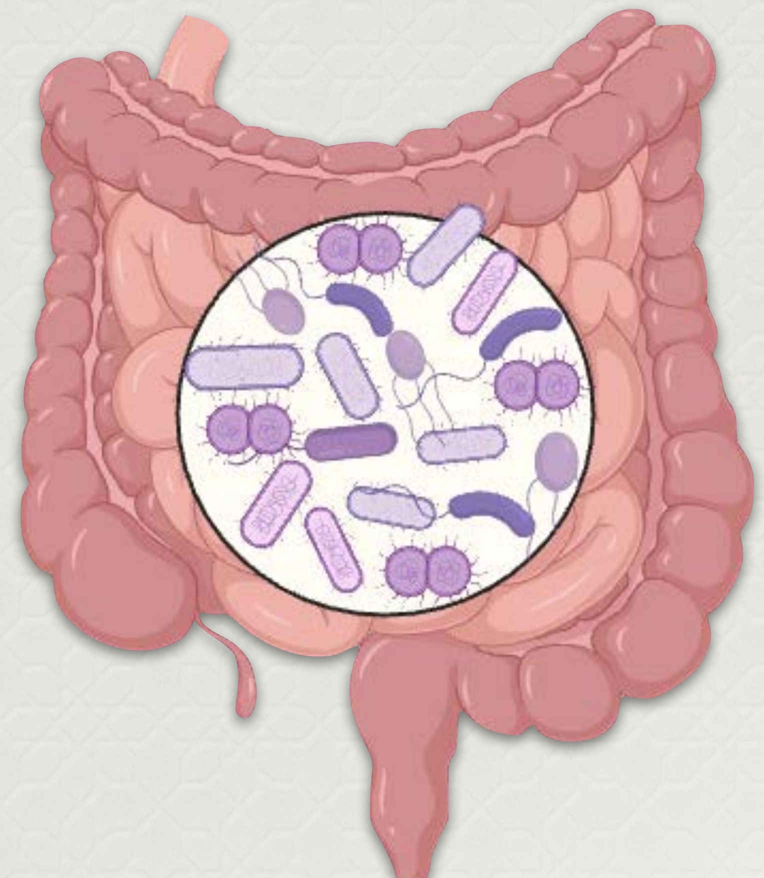
Oxalate in Humans



OXALATE ABSORPTION 10 - 15%

Intake critical for
Oxalate homeostasis

Up to 98%
used by gut bacteria
for energy

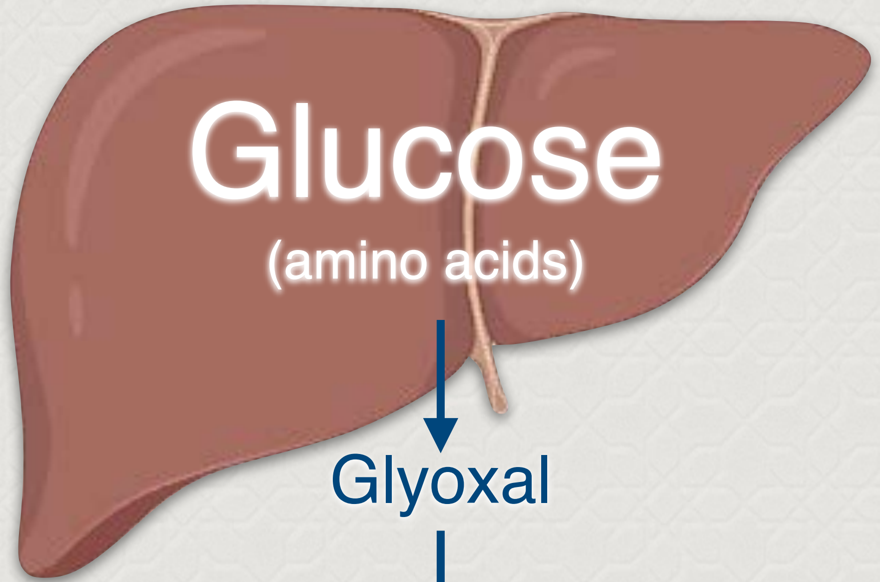


Calcium binds to make
Oxalate insoluble =
crystalline

5 -10%
Excreted in feces

Oxalate Homeostasis in Non-Stone-Forming Chronic Kidney Disease…Stepanova, N., 2023

OXALATE PRODUCTION 60 - 80%



↓

Glyoxal

↓

Glyoxylate

↓

OXALATE

↓

URINARY OXALATE

Glyoxal Formation and Its Role in Endogenous Oxalate Synthesis, Lange, J., et al., 2012

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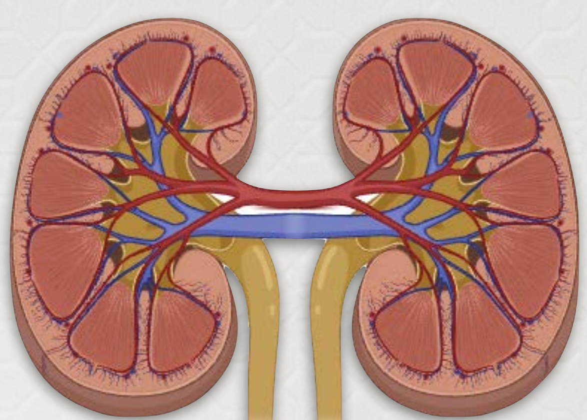
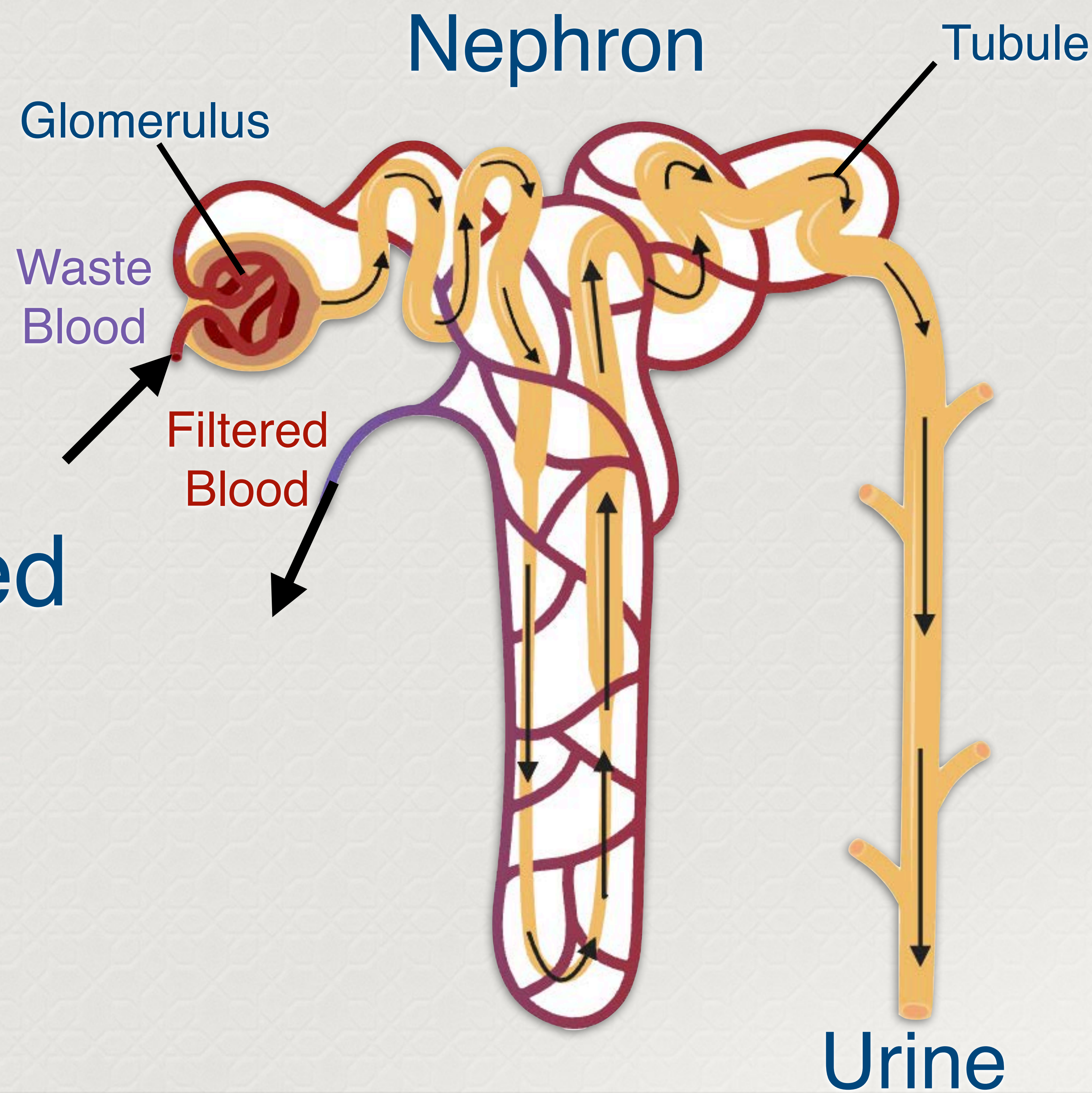
OXALATE EXCRETION

~ **95%**

Oxalate Excreted

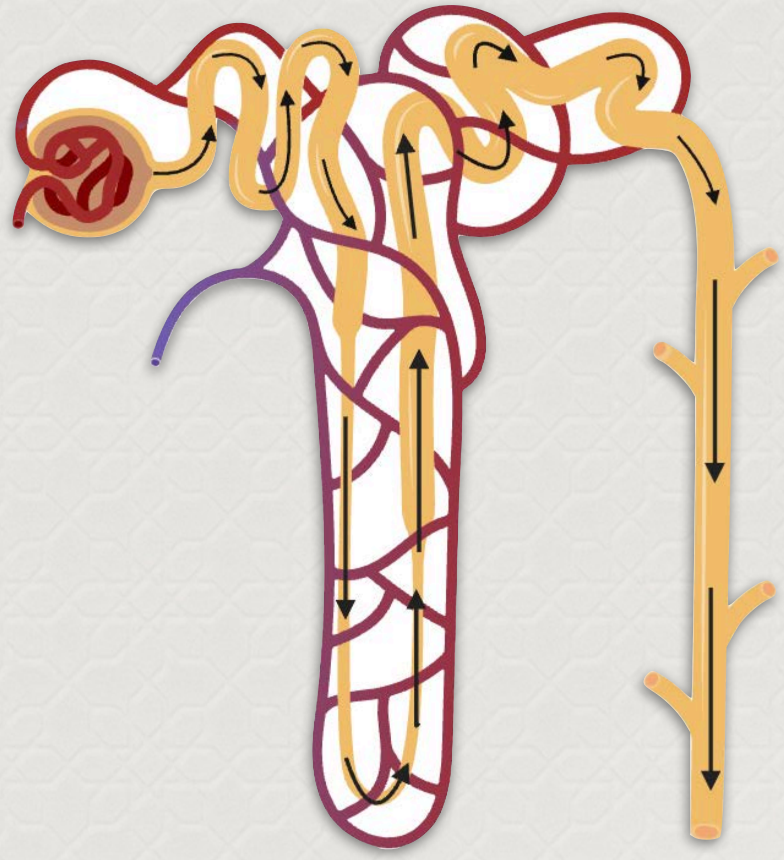
via





HEALTHY KIDNEYS

Nephron



Glomerular Filtration Rate
(GFR) > 90 mL/min

GFR ⬇ 1% per year after age 40

Nephron number varies by individual

Total nephron number set in utero by 36 weeks

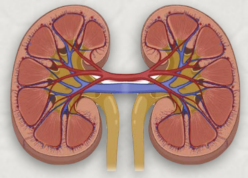
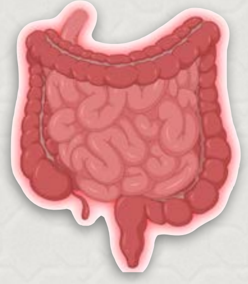
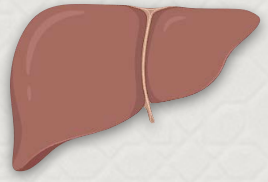
Human nephron number, hypertension, and renal pathology. Kanzaki, G., et al., 2020

Oxalate dysfunction in humans?

OXALATE ACCUMULATION

Hyperoxaluria

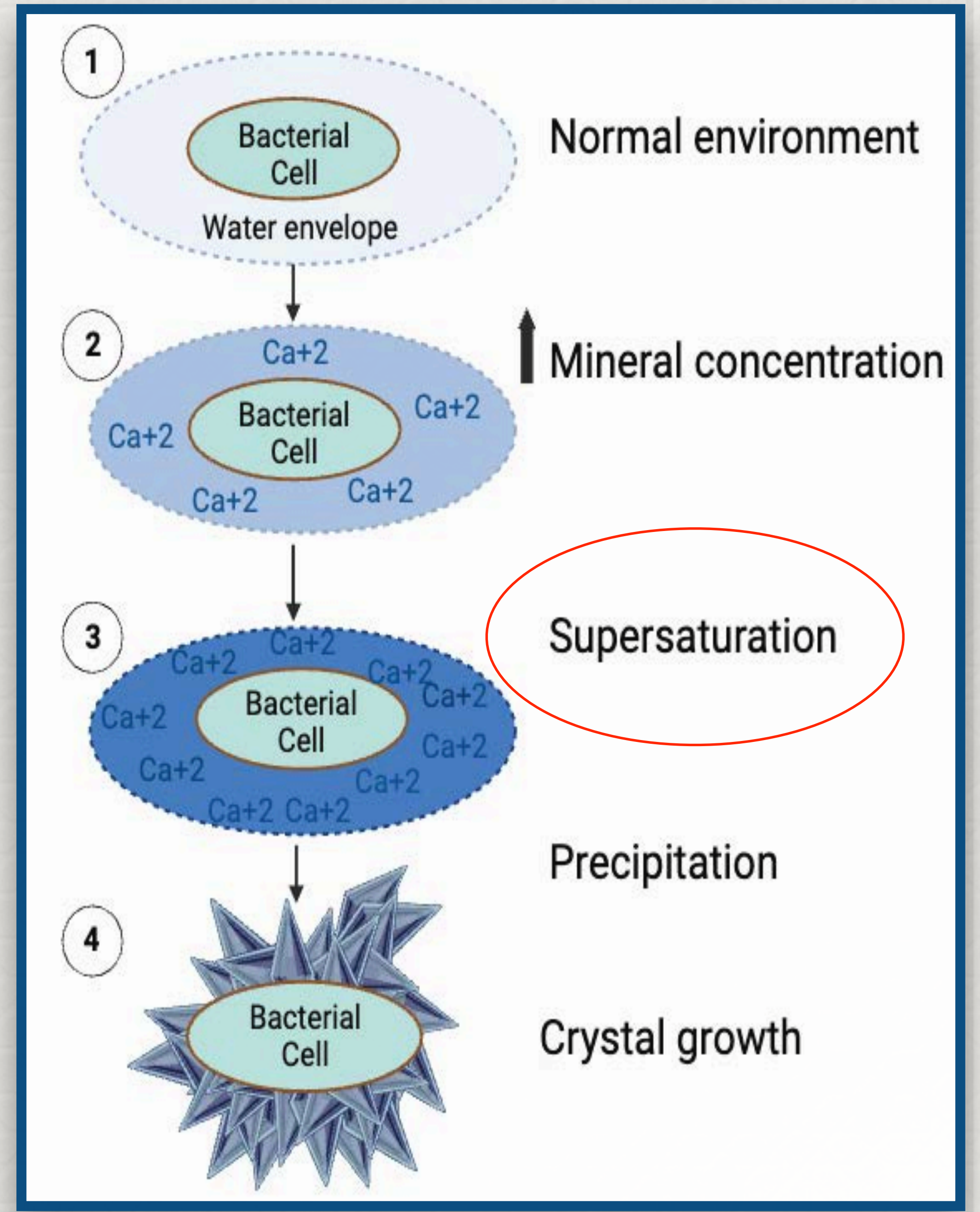
Pathways to hyperoxaluria:

1. ⬇ kidney function - supersaturation 
2. ⬆ intestinal absorption 
3. ⬆ liver production 

Contribution of Dietary Oxalate and Oxalate Precursors to Urinary Oxalate Excretion. Crivelli, J., et al., 2020

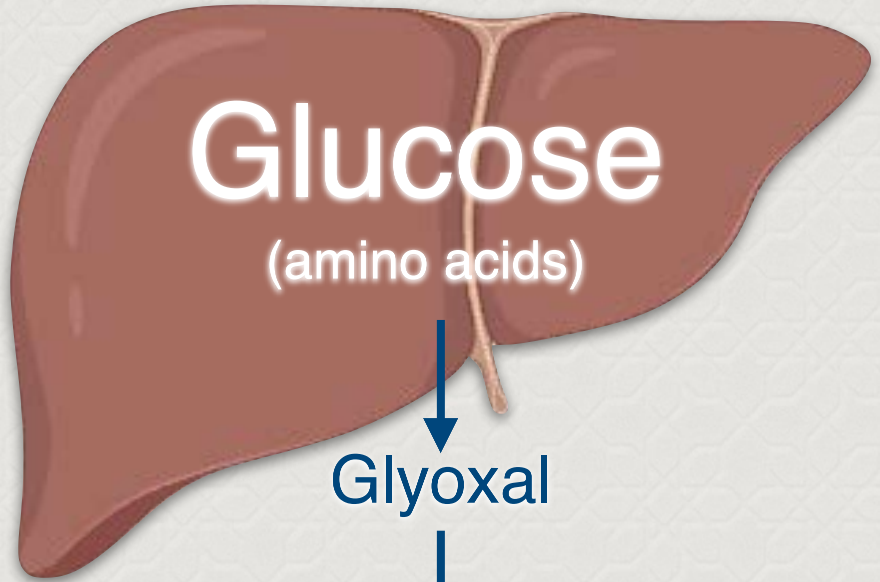
Supersaturation

- Driving force for CaOx crystal growth
- Main risk factor for stone formation
- Linked to low water intake



Contribution of Dietary Oxalate and Oxalate Precursors to Urinary Oxalate Excretion. Crivelli, J., et al., 2020

OVER - PRODUCTION



Glucose

(amino acids)

↓

Glyoxal

↓

Glyoxylate → Marker for Diabetes and Obesity

↓

OXALATE

↓

URINARY OXALATE

Glyoxal Formation and Its Role in Endogenous Oxalate Synthesis, Lange, J., et al., 2012

Hindawi Publishing Corporation
Journal of Diabetes Research
Volume 2014, Article ID 685204, 9 pages
http://dx.doi.org/10.1155/2014/685204

Hindawi

2014

Research Article

Glyoxylate, a New Marker Metabolite of Type 2 Diabetes

Victoria J. Nikiforova,[1,2] Pieter Giesbertz,[3] Jan Wiemer,[4,5] Bianca Bethan,[4] Ralf Looser,[4] Volker Liebenberg,[1,5] Patricia Ruiz Noppinger,[1,6] Hannelore Daniel,[3] and Dietrich Rein[1]

Glyoxylate plasma levels

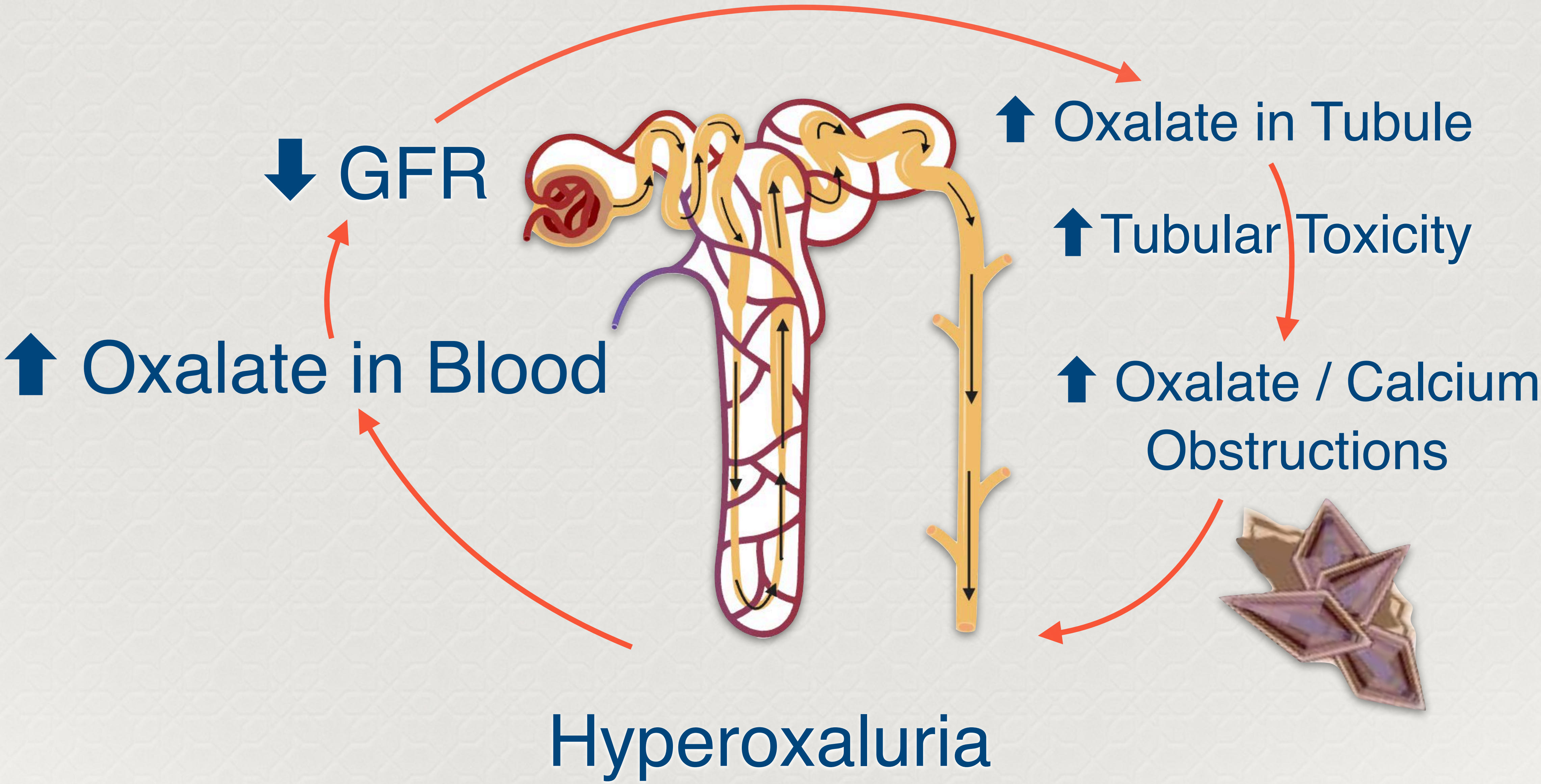
- predict diabetes up to 3 years before diagnosis

Urinary oxalate excretion

- is linked to diabetes independent of dietary oxalate intake
- elevated in both obesity and diabetes from ⬆generation and absorption

Diabetes and Obesity = ⬆ Oxalate in Blood

⬆ Production ⬆ Absorption



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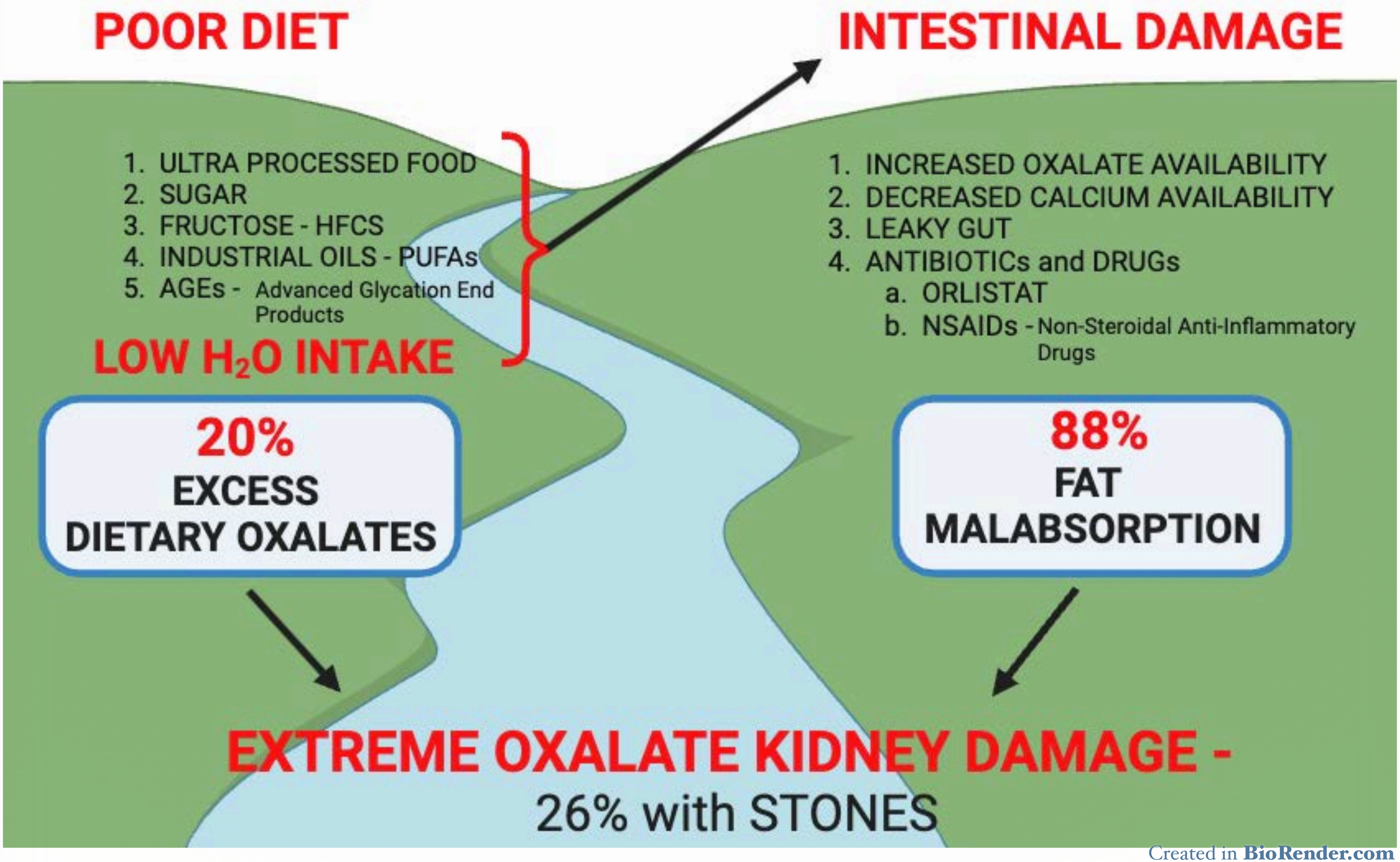
Urinary oxalate as a potential mediator of kidney disease in diabetes mellitus and obesity. Efe, O., et al., 2019

HYPEROXALURIA

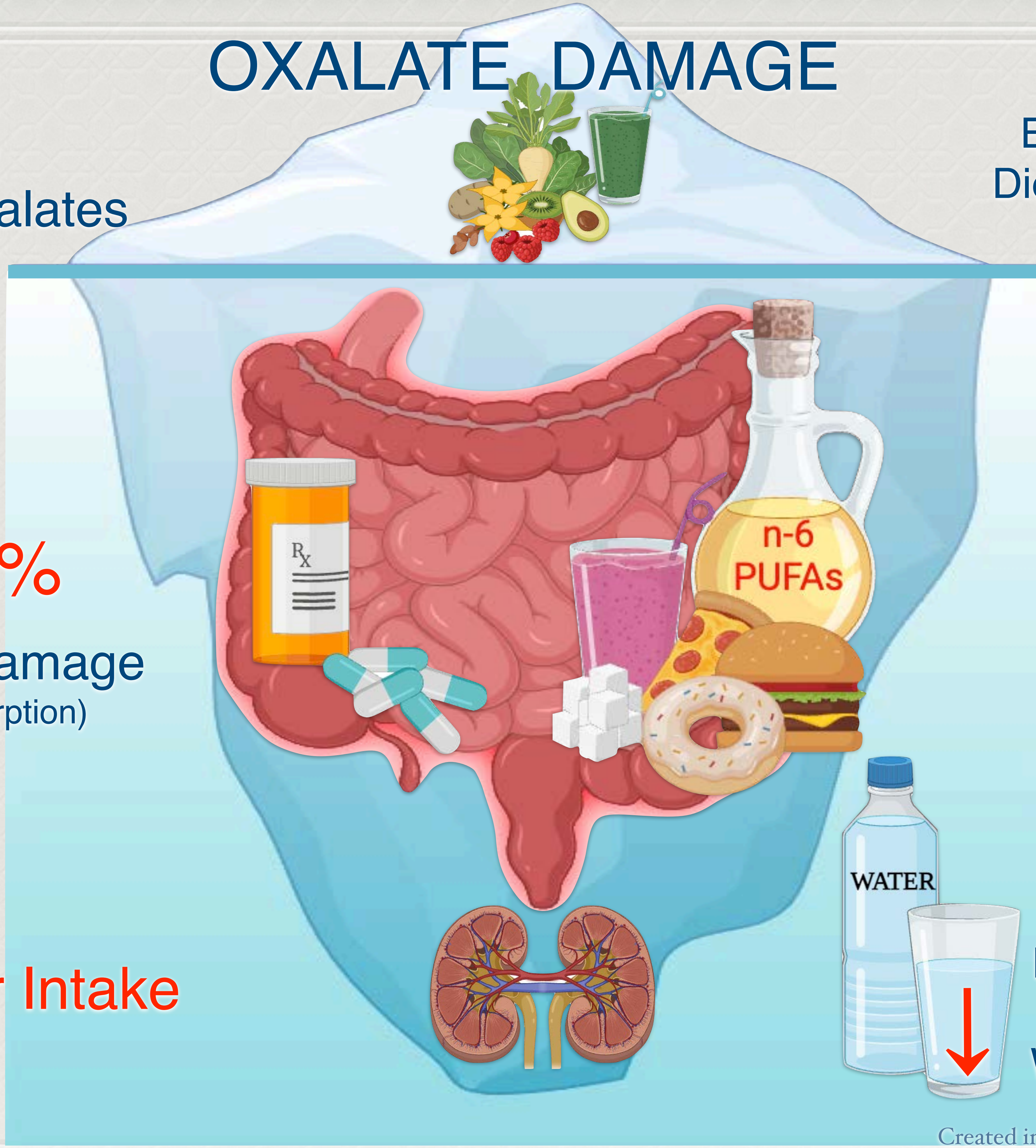


Secondary Oxalate Nephropathy: A Systematic Review. Lumlertgul, N., et al. 2018;
Hydration Biomarkers Are Related to the Differential Abundance of Fecal Microbiota… Willis, N., et al., 2021

OXALATE DAMAGE

20%
Dietary Oxalates

Weak Evidence for Dietary Oxalate Restriction

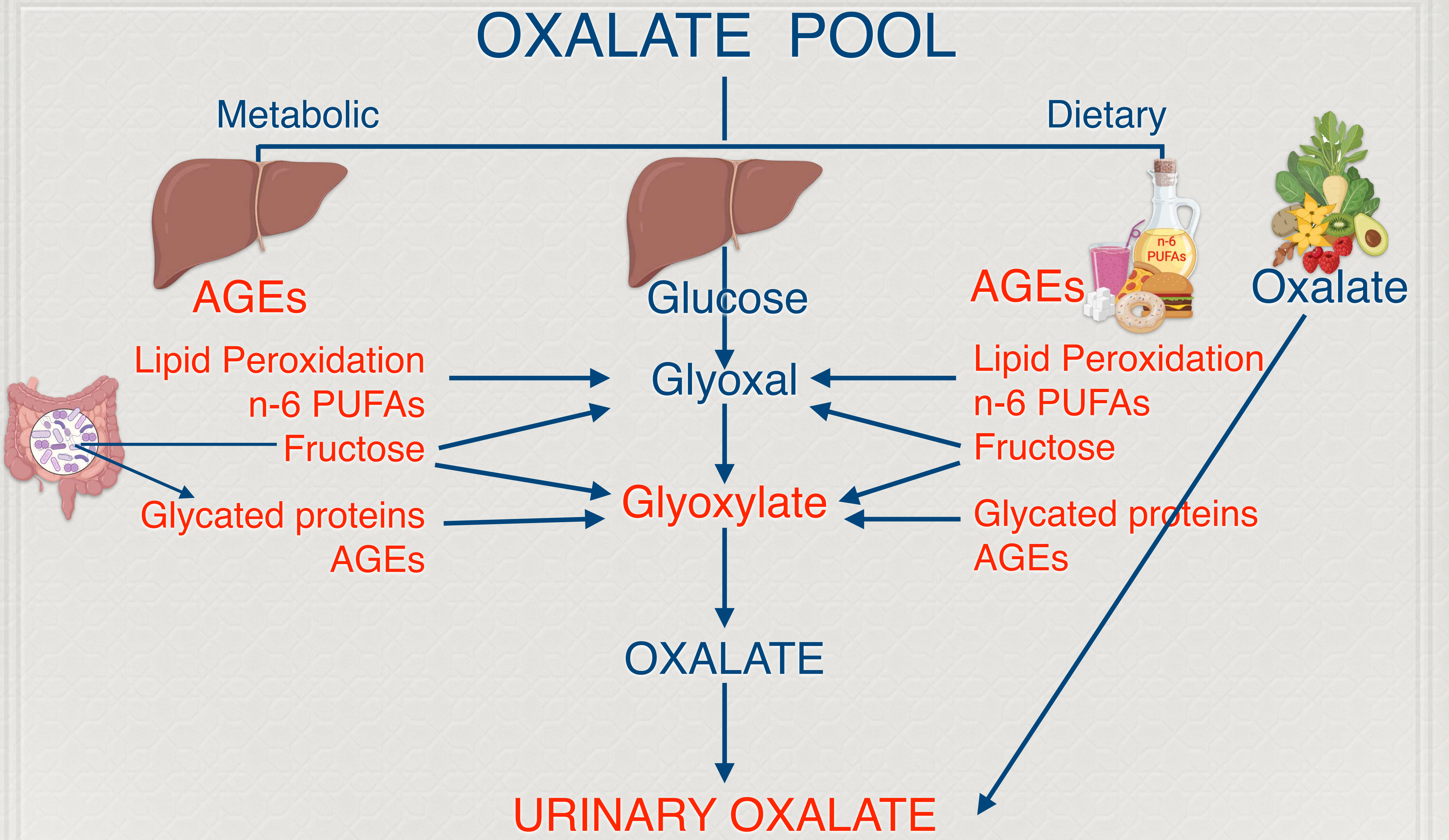


88%
Intestinal Damage
(Fat Malabsorption)

Low Water Intake

Strong Evidence for Low Water Intake

Diet and Stone Disease in 2022, Dai, J., & Pearle, M., 2022; The Use of Antibiotics and Risk of Kidney Stones, Joshi, S., & Goldfarb, D., 2019



Glyoxal Formation and Its Role in Endogenous Oxalate Synthesis, Lange, J., et al., 2012

Ultra-Processed Food

> 60% of US daily diet

AGEs - Gut

Dysbiosis
Gut inflammation

AGEs - Kidneys

Accumulation
Damage nephron

AGEs - Systemic

Accumulation and Damage
in every organ

Role of gut microbiota in the modulation of the health effects of advanced glycation end-products (Review).
Aschner,M., et al., 2023

ANTIBIOTICS

Antibiotics cause rapid loss of microbial oxalate metabolism

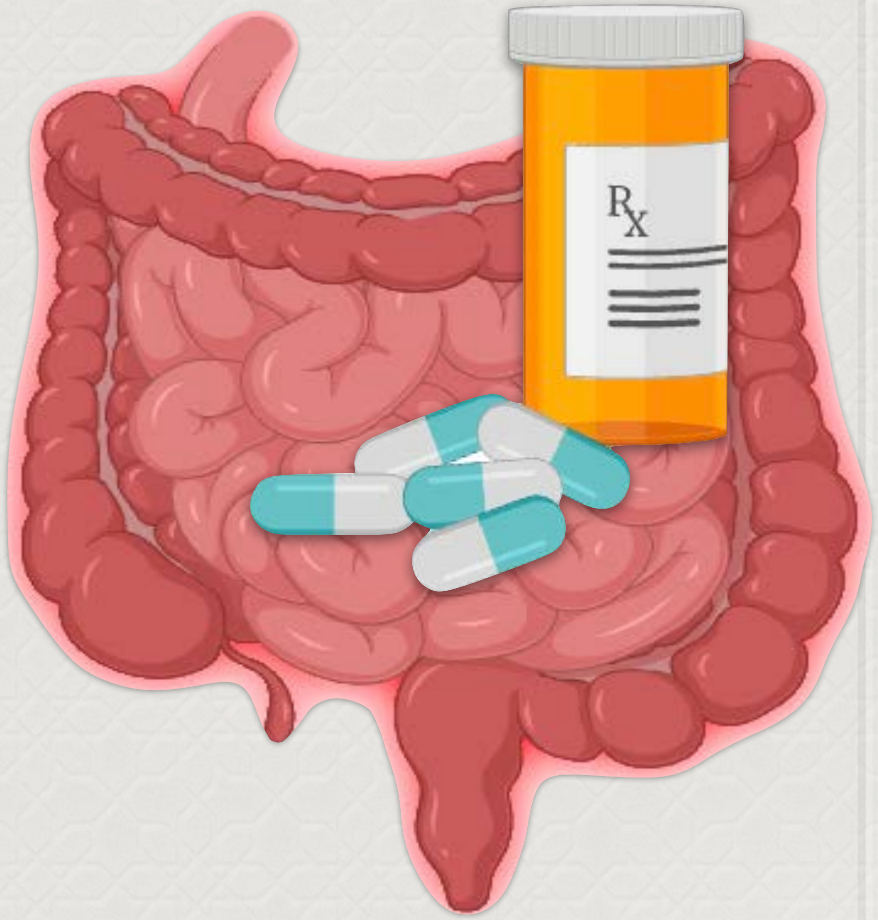
63% elimination of Oxalobacter formigenes after 2-week course

Limited or no recovery of Oxalate metabolism

Strongly linked to risk of kidney stones

70% of CaOx stones contain multi-antibiotic resistant bacteria

Direct antibiotic crystalization of stone formation?

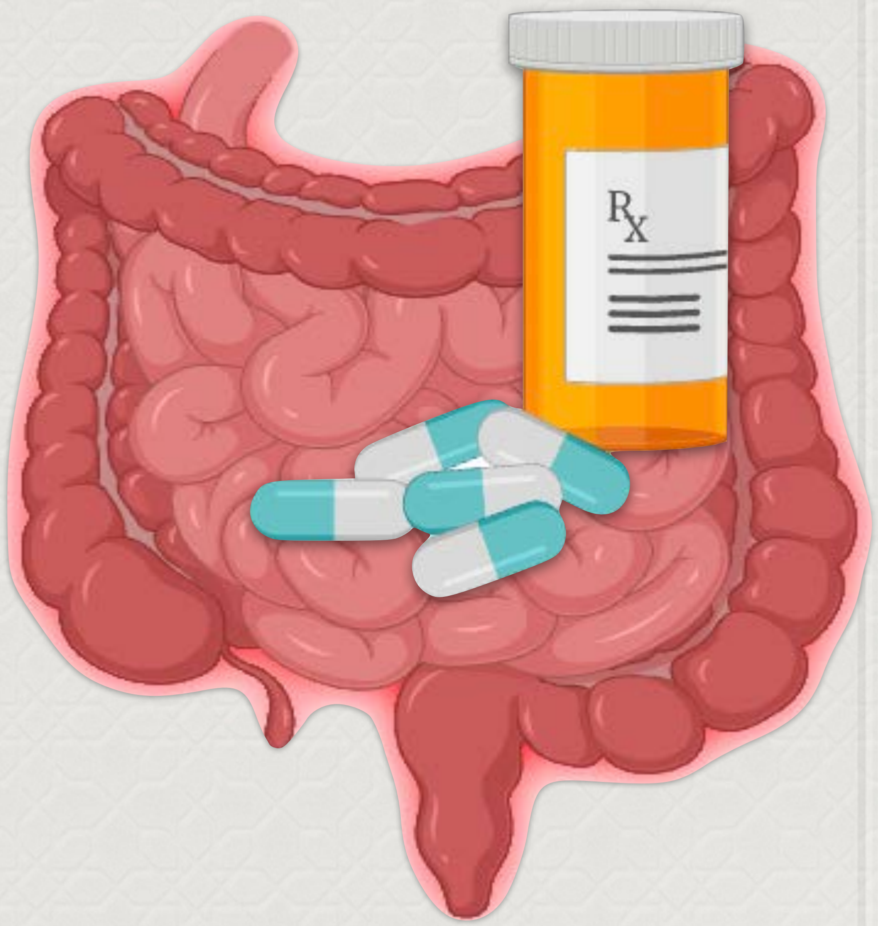


The Use of Antibiotics and Risk of Kidney Stones. Joshi, 2019

OTHER DRUGS

Drugs that disturb gut bacteria -

NSAIDs
osmotic laxatives
hormones
benzodiazepines
antidepressants
antihistamines
IBD drugs
proton pump inhibitors
metformin
statins
psychotropic drugs

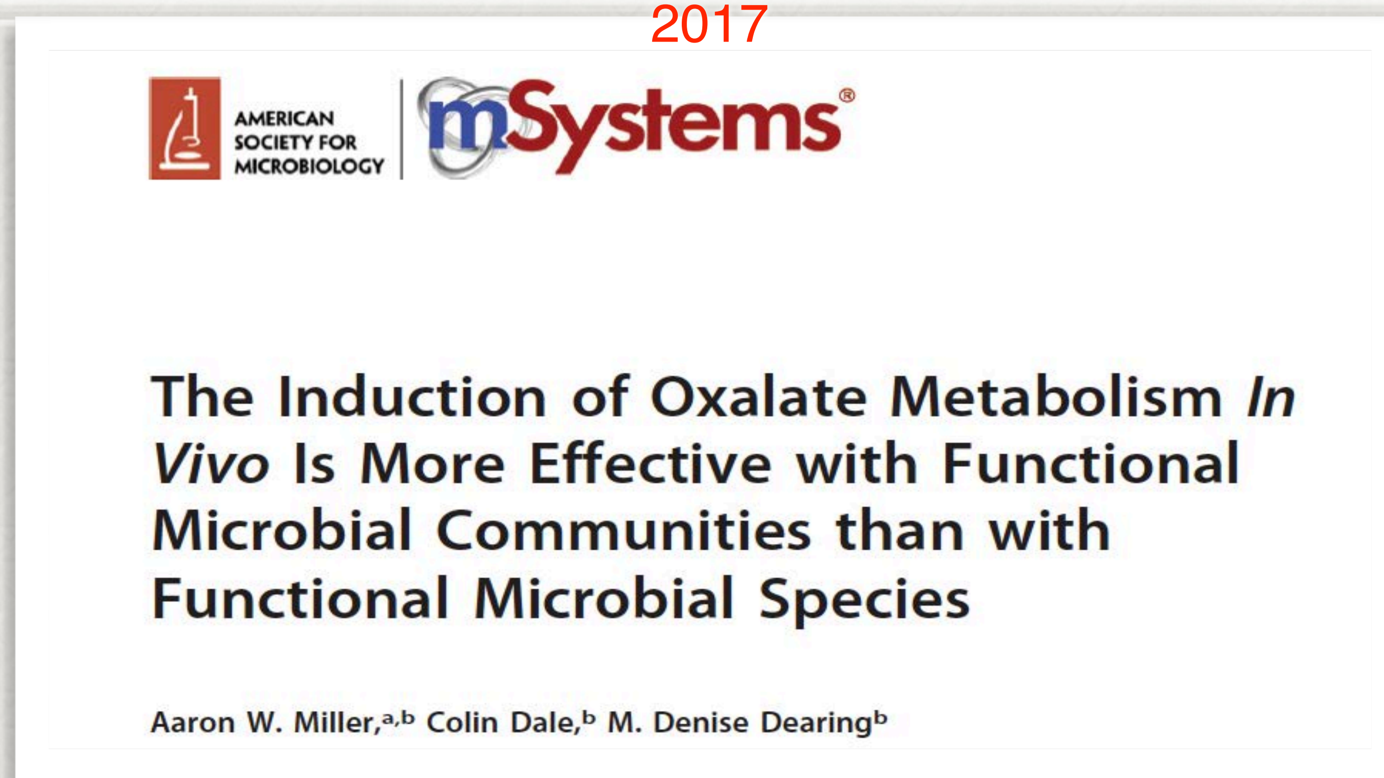


> 30 drugs are substrates of gut bacterial enzymes

Microbiota in health and diseases. Hou, K., et al., 2022

Oxalate Degrading Network

2017



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The Induction of Oxalate Metabolism *In Vivo* Is More Effective with Functional Microbial Communities than with Functional Microbial Species

Aaron W. Miller,[a,b] Colin Dale,[b] M. Denise Dearing[b]

Oxalate consumption stimulates a wide range of bacteria, which degrade 100% of consumed Oxalate

Animals receiving N. albigula fecal transplants display similar oxalate-degrading potential for up to 9 months

N. albigula

2022

foods

MDPI

Review

Probiotic Oxalate-Degrading Bacteria: New Insight of Environmental Variables and Expression of the oxc and frc Genes on Oxalate Degradation Activity

Dina Karamad [1], Kianoush Khosravi-Darani [1,*], Amin Mousavi Khaneghah [2] and Aaron W. Miller [3]

Oxalate-degrading bacteria, when present in the GIT tract are able to decrease urine oxalate up to 40% and significant reduction of oxalate stone formation in the kidneys.

Bifidobacterium (B.) spp. and Lactobacillus (L.) spp. have the ability of degradation oxalate into carbon dioxide and formate

Probiotic Oxalate-Degrading Bacteria: Karamad, D., et al., 2022

2021

eLife

RESEARCH ARTICLE

Microbial genetic and transcriptional contributions to oxalate degradation by the gut microbiota in health and disease

Menghan Liu[1,2†], Joseph C Devlin[1,2], Jiyuan Hu[1], Angelina Volkova[1,2], Thomas W Battaglia[1], Melody Ho[1], John R Asplin[3], Allyson Byrd[4], P'ng Loke[1], Huilin Li[1], Kelly V Ruggles[1], Aristotelis Tsirigos[1], Martin J Blaser[5]*, Lama Nazzal[1]*

Oxalate degradation has been known since the 1940s but never described

Focus has been on O. formigenes

First comprehensive study to characterize oxalate-degrading bacteria in vivo with > 1000 subjects

The majority (92 %) of healthy gut microbiomes include oxalate degrading enzymes

Microbial genetic and transcriptional contributions to oxalate degradation by the gut microbiota in health and disease. Liu, M., et al., 2020

Guiding Thoughts

Tragic Oxalate Overdose

Supersaturation
No water

Loss of tolerance
10x legal dose

Utah, 1971

EPA, The January 1971 Sheep Death Incident Near Garrison, Utah. 1971, US Atomic Energy Commission: Radiological Research Program.

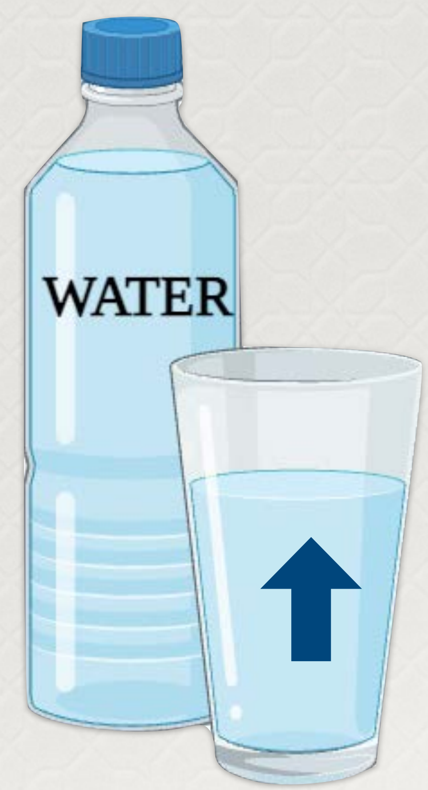
Increased water intake is the universally recognized therapeutic approach for reducing the risk of kidney stones

- 65% adults under-hydrated due to low water intake
- Poor hydration status linked to intestinal inflammation

⬆ Water intake to 2 to 3 L per 24 hours

Drink before bed and again during the night

Keep hydrated to prevent fluid loss



Epidemiology of Kidney Stones. Stamatelou, K., & Goldfarb, D., 2023
Nutrition and kidney stone disease. Siener, R., 2021
Hydration Biomarkers Are Related to the Differential Abundance. Willis, N., et al., 2021

Bicarbonate helps eliminate Oxalate

Gerolsteiner Mineral Content mg/L

Bicarbonate	1816
Calcium	384
Magnesium	108

2 L/day of mineral water containing 1715 mg/L bicarbonate significantly increased urine pH and citrate excretion and decreased oxalate excretion

Mineral water bicarbonate determines the risk of stone formation

https://www.gerolsteiner-usa.com/home

2019

EBioMedicine 45 (2019) 231–250

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Dietary vinegar prevents kidney stone recurrence via epigenetic regulations

Wei Zhu [a,1], Yang Liu [a,1], Yu Lan [a,1], Xiaohang Li [a,1], Lianmin Luo [a], Xiaolu Duan [a], Ming Lei [a], Guanzhao Liu [a], Zhou Yang [a], Xin Mai [a], Yan Sun [c], Li Wang [c], Suilin Lu [a], Lili Ou [a], Wenqi Wu [a], Zanlin Mai [a], Dongliang Zhong [a], Chao Cai [a], Zhijian Zhao [a], Wen Zhong [a], Yongda Liu [a], Yin Sun [a,b,*], Guohua Zeng [a,**]

Acetic acid 5% reduces KSD risk
5 ml dose 3x/day

60% decreased risk

Chinese study of > 9000 people

Dietary vinegar prevents kidney stone recurrence via epigenetic regulations. Zhu, W., et al., 2019

2021

Archives of Microbiology
https://doi.org/10.1007/s00203-021-02484-3

ORIGINAL PAPER

Check for updates

Activity of probiotics from food origin for oxalate degradation

Nariman R. Soliman[1] · Baher A. M. Effat[1] · Nayra Sh. Mehanna[1] · Nabil F. Tawfik[1] · Mohamed K. Ibrahim[2]

The gut microbiota consumes oxalate to maintain oxalate homeostasis

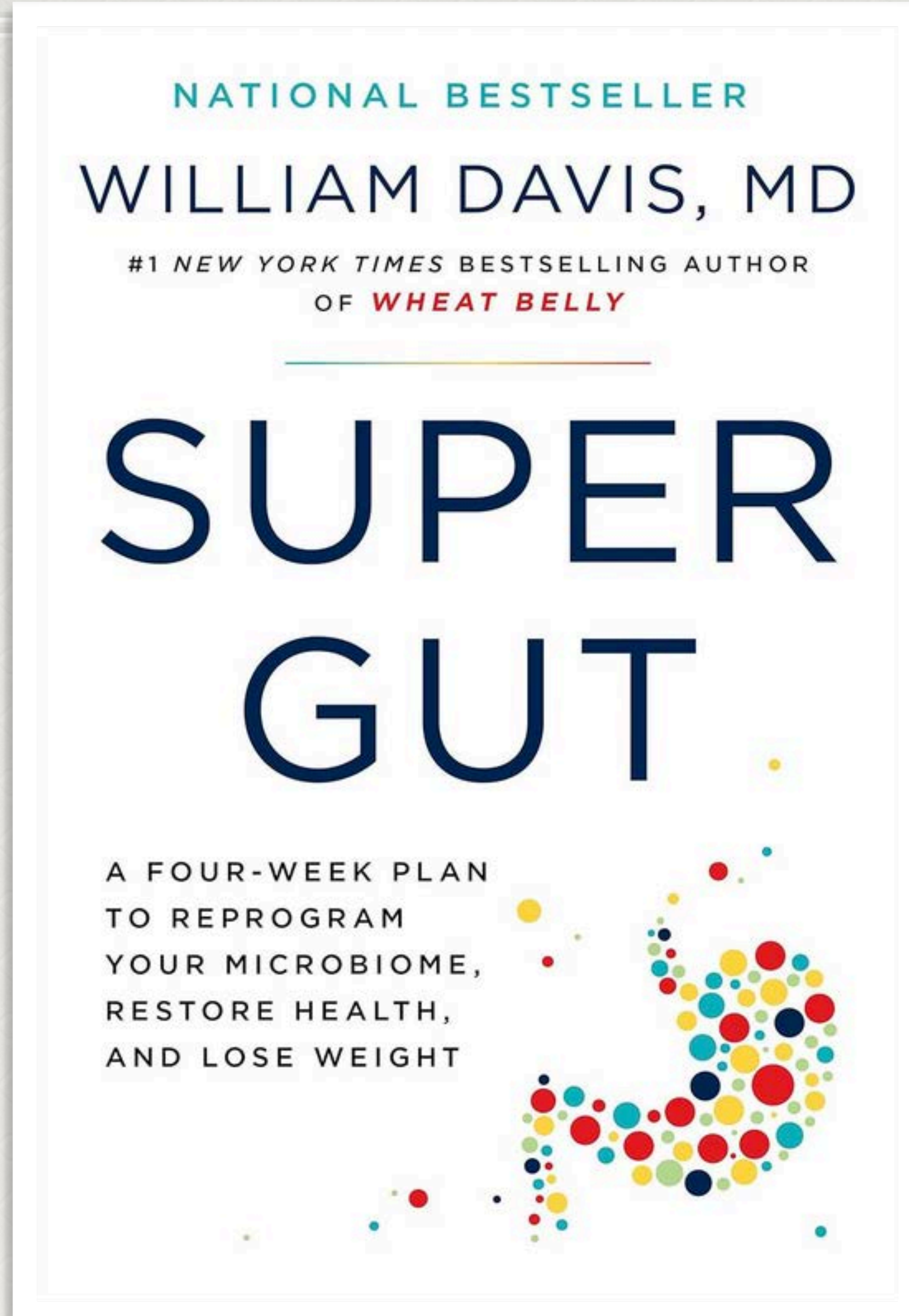
7 strains of Lactobacillus spp. were isolated from dairy products

These strains showed oxalate-degrading ability plus

- Ability to tolerate acid, bile salts, and phenol
- Antibiotic-resistant to a wide range of antibiotics

Lactobacillus acidophilus and Lactobacillus gasseri, showed significant oxalate degradation activity

Activity of probiotic from food origin for oxalate degradation. Soliman, N., et al., 2021


NATIONAL BESTSELLER
WILLIAM DAVIS, MD
#1 NEW YORK TIMES BESTSELLING AUTHOR OF WHEAT BELLY
SUPER GUT
A FOUR-WEEK PLAN TO REPROGRAM YOUR MICROBIOME, RESTORE HEALTH, AND LOSE WEIGHT

Future Developments

Fecal Microbiota Transplant (FMT)

Drug Therapy

Reloxaliase (formerly known as ALLN-177) is a recombinant oxalate decarboxylase

Enzyme used by O. formigenes to degrade oxalate

A randomized trial to be completed in November 2023

Oxadrop is a probiotic composed of Lactobacillus acidophilus, Lactobacillus brevis, Streptococcus thermophilus and Bifidobacterium infantis

Oxalate nephropathy: a review, Rosenstock, J.L., et al., 2021

Thank you!

dr.ruthannfoster@gmail.com

REFERENCES

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SOURCES

1. Ahmed, F. and A. Mohammed, *Magnesium: The Forgotten Electrolyte-A Review on Hypomagnesemia.* Med Sci (Basel), 2019. **7**(4).
2. Sakaguchi, Y., *The emerging role of magnesium in CKD.* Clinical and experimental nephrology, 2022. **26**(5): p. 379-384.
3. López, M. and B. Hoppe, *History, epidemiology and regional diversities of urolithiasis.* Pediatric nephrology, 2010. **25**: p. 49-59.
4. Peerapen, P. and V. Thongboonkerd, *Kidney stone prevention.* Advances in Nutrition, 2023.
5. Sivaguru, M., et al., *Human kidney stones: a natural record of universal biomineralization.* Nature Reviews Urology, 2021. **18**(7): p. 404-432.
6. Saw, J.J., et al., *In vivo entombment of bacteria and fungi during calcium oxalate, brushite, and struvite urolithiasis.* Kidney360, 2021. **2**(2): p. 298.
7. Wang, Z., et al., *Recent advances on the mechanisms of kidney stone formation (Review).* Int J Mol Med, 2021. **48**(2): p. 149.
8. Joshi, S. and D.S. Goldfarb, *The use of antibiotics and risk of kidney stones.* Current opinion in nephrology and hypertension, 2019. **28**(4): p. 311.
9. Haran, J.P. and B.A. McCormick, *Aging, frailty, and the microbiome—how dysbiosis influences human aging and disease.* Gastroenterology, 2021. **160**(2): p. 507-523.
10. David, L.A., et al., *Diet rapidly and reproducibly alters the human gut microbiome.* Nature, 2014. **505**(7484): p. 559-563.
11. Chmiel, J.A., et al., *Vitamins as regulators of calcium-containing kidney stones—new perspectives on the role of the gut microbiome.* Nature Reviews Urology, 2023: p. 1-23.
12. Miller, A.W., et al., *Loss of function dysbiosis associated with antibiotics and high fat, high sugar diet.* Isme j, 2019. **13**(6): p. 1379-1390.
13. Hou, K., et al., *Microbiota in health and diseases.* Signal Transduction and Targeted Therapy, 2022. **7**(1): p. 135.
14. Reinhard, K.J. and D.R. Danielson, *Pervasiveness of phytoliths in prehistoric southwestern diet and implications for regional and temporal trends for dental microwear.* Journal of Archaeological Science, 2005. **32**(7): p. 981-988.
15. Riley, T., *Ethnohistoric Records of Hunter-Gatherer Diet of the Texas/Mexico Borderlands: Implications for Staple Foods of the Lower Pecos Canyonlands During the Holocene.* Index of Texas Archaeology: Open ***19****(2): p. 123-138.*

16. Miller, A.W., C. Dale, and M.D. Dearing, *The induction of oxalate metabolism in vivo is more effective with functional microbial communities than with functional microbial species.* MSystems, 2017. **2**(5): p. 10.1128/msystems. 00088-17.
17. Kuhnlein, H. and N. Turner, *Traditional plant foods of Canadian indigenous peoples: nutrition, botany and use*. 2020: Routledge.
18. Wakhanu, A., J. Kimiywe, and H. Nyambaka, *Oxalate levels in selected African indigenous vegetable recipes from the lake victoria basin, Kenya.* International Journal of Agriculture and Environmental Research, 2015. **1**(2): p. 88-105.
19. García-Herrera, P., et al., *Nutritional and Phytochemical Composition of Mediterranean Wild Vegetables after Culinary Treatment.* Foods, 2020. **9**(12): p. 1761.
20. Syed, S., V. Buddolla, and B. Lian, *Oxalate carbonate pathway—Conversion and fixation of soil carbon —A potential scenario for sustainability.* Frontiers in Plant Science, 2020. **11**: p. 591297.
21. Gadd, G.M., et al., *Oxalate production by fungi: significance in geomycology, biodeterioration and bioremediation.* Fungal Biology Reviews, 2014. **28**(2): p. 36-55.
22. Martin, G., et al., *Fungi, bacteria and soil pH: the oxalate–carbonate pathway as a model for metabolic interaction.* Environmental microbiology, 2012. **14**(11): p. 2960-2970.
23. Ermer, T., et al., *Oxalate homeostasis.* Nature Reviews Nephrology, 2023. **19**(2): p. 123-138.
24. Stepanova, N., *Oxalate Homeostasis in Non-Stone-Forming Chronic Kidney Disease: A Review of Key Findings and Perspectives.* Biomedicines, 2023. **11**(6): p. 1654.
25. Lange, J.N., et al., *Glyoxal formation and its role in endogenous oxalate synthesis.* Advances in urology, 2012. **2012**.
26. Kanzaki, G., et al., *Human nephron number, hypertension, and renal pathology.* The Anatomical Record, 2020. **303**(10): p. 2537-2543.
27. Crivelli, J.J., et al., *Contribution of dietary oxalate and oxalate precursors to urinary oxalate excretion.* Nutrients, 2020. **13**(1): p. 62.
28. Nikiforova, V.J., et al., *Glyoxylate, a new marker metabolite of type 2 diabetes.* Journal of diabetes research, 2014. **2014**.
29. Efe, O., A. Verma, and S.S. Waikar, *Urinary oxalate as a potential mediator of kidney disease in diabetes mellitus and obesity.* Curr Opin Nephrol Hypertens, 2019. **28**(4): p. 316-320.
30. Lumlertgul, N., et al., *Secondary oxalate nephropathy: a systematic review.* Kidney international reports, 2018. **3**(6): p. 1363-1372.

31. Willis, N.B., et al., *Hydration biomarkers are related to the differential abundance of fecal microbiota and plasma lipopolysaccharide-binding protein in adults.* Annals of Nutrition and Metabolism, 2021. **77**(Suppl. 4): p. 37-45.
32. Dai, J.C. and M.S. Pearle, *Diet and Stone Disease in 2022.* Journal of Clinical Medicine, 2022. **11**(16): p. 4740.
33. Aschner, M., et al., *Role of gut microbiota in the modulation of the health effects of advanced glycation end-products.* International journal of molecular medicine, 2023. **51**(5): p. 1-12.
34. Karamad, D., et al., *Probiotic Oxalate-Degrading Bacteria: New Insight of Environmental Variables and Expression of the oxc and frc Genes on Oxalate Degradation Activity.* Foods, 2022. **11**(18): p. 2876.
35. Liu, M., et al., *Microbial genetic and transcriptional contributions to oxalate degradation by the gut microbiota in health and disease.* Elife, 2021. **10**: p. e63642.
36. EPA, *The January 1971 Sheep Death Incident Near Garrison, Utah*. 1971, US Atomic Energy Commission: Radiological Research Program.
37. Stamatelou, K. and D.S. Goldfarb. *Epidemiology of kidney stones*. in *Healthcare*. 2023. MDPI.
38. Siener, R., *Nutrition and kidney stone disease.* Nutrients, 2021. **13**(6): p. 1917.
39. Zhu, W., et al., *Dietary vinegar prevents kidney stone recurrence via epigenetic regulations.* EBioMedicine, 2019. **45**: p. 231-250.
40. Soliman, N.R., et al., *Activity of probiotics from food origin for oxalate degradation.* Archives of Microbiology, 2021. **203**: p. 5017-5028.
41. Rosenstock, J.L., et al., *Oxalate nephropathy: a review.* Clinical Kidney Journal, 2021. **15**(2): p. 194-204.