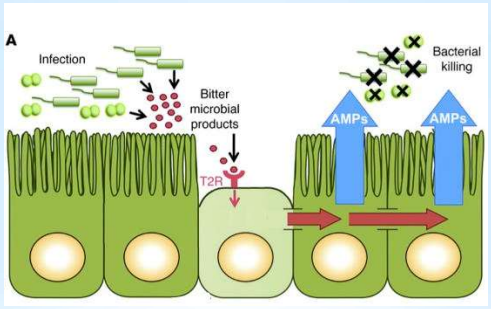


Bitter herbs in mucosal immunity

Updates on T2Rs: locations, influence, and therapeutic implications. Innate immunity update.

1

- The "mucosa": lines all hollow organs
- Respiratory mucosa: primary focus for many
  - Allergies (allergic rhinitis)
    - 20 mil adults, 6 mil children
  - Asthma (reactive airway)
    - 20 mil adults, 6 mil children
  - Respiratory infection (viral / bacterial)
  - Chronic bacterial colonization (sinusitis)
    - 30.8 million adults

Scope

Statistics: CDC 2017

2

*The "mucosa": lines all hollow organs

*Respiratory mucosa: primary focus for many

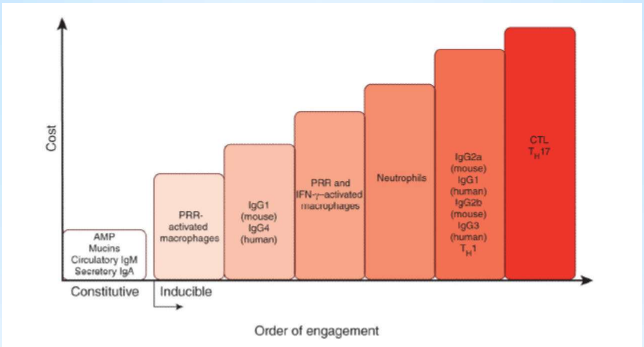
*Treatment options include steroids, anti-inflammatories, bronchodilators, antibiotics

… with mixed success, esp. in chronic conditions

*Scope

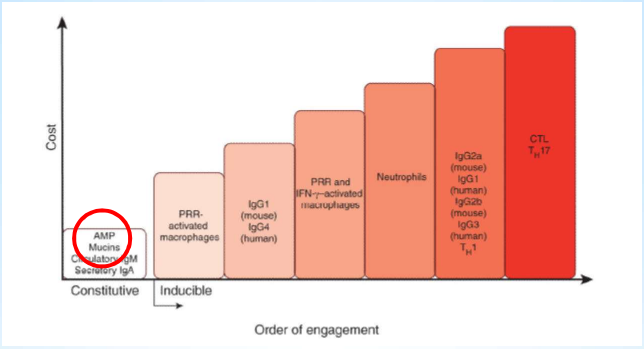
Can we do better?
Can we work with the body's own defenses?

3



Innate Immunity Update: WHY allergy, hyperreactivity?
Order of engagement/cost of response:
Allergy is a low-cost, rapid response. Immunity is less effective without it ("Control of adaptive immunity by the innate immune system", Medzhitov 2015)

4



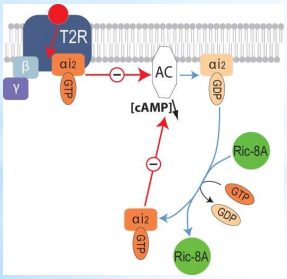
Innate Immunity Update:
Order of engagement/cost of response:

Our job is to select the pieces of constitutive, mucosal immunity that support defenses, while reducing the "triggering" to prevent hyperreactivity.

AMPs = AntiMicrobial Peptides (more later)

5

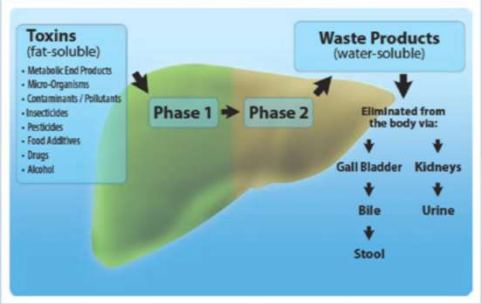
* First isolated and described on the tongue
* Complex – sensitive to 120+ chemical triggers
* Important regulator of digestive function and secretions across the GI mucous membrane
* …. And beyond?



*The bitter taste receptor (T2R)

6

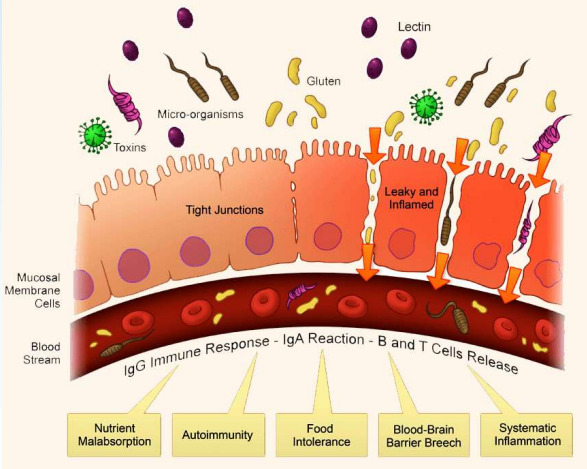
* Crucial metabolic organ – breakdown and recombination of waste, toxins
* Can contribute to inflammation across the physiology (cardio, GI, neuro, respiratory)



*The Liver

7

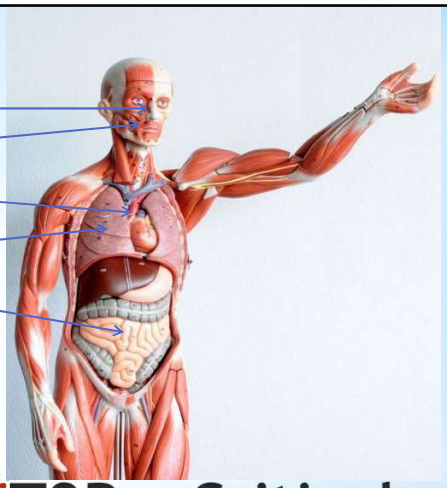
* Permeability can change for a range of reasons – notably, inflammation ("leaky gut")
* High mucosal permeability increases inflammation across the physiology



*The GI tract mucosa

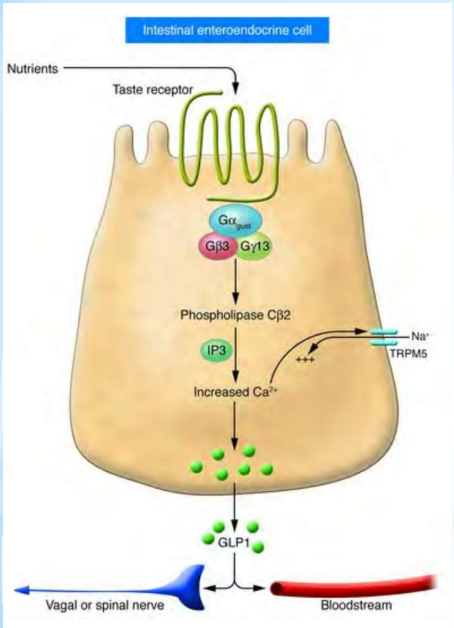
8

*Upper Airway
*Tongue
*Cardiovascular system
*Lower airway
*Intestinal tract



*T2Rs: Critical locations

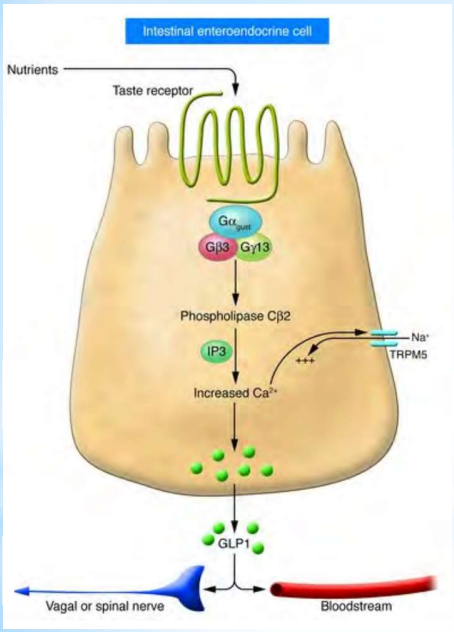
9



*Intestine/stomach mostly
*Enteroendocrine cells secrete PYY, GLP-1, gastric motility paracrines, immune-active cytokines (TNF-α, e.g.) (Komarnytsky 2015)

*Endocrine relay

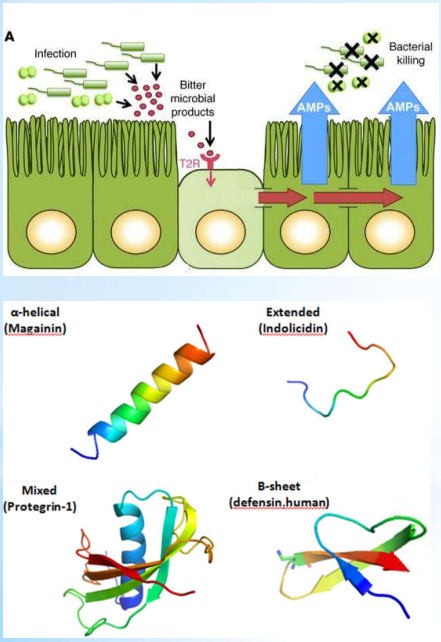
10



* **Intestine/stomach mostly**
* Hormones/paracrines affect:
  * Satiety (PYY, GLP1)
  * Motility (CCK, NO)
  * Secretion (Batterham 2017)
  * Immunology: inflammation reduced (Worthington 2018)

*Endocrine relay

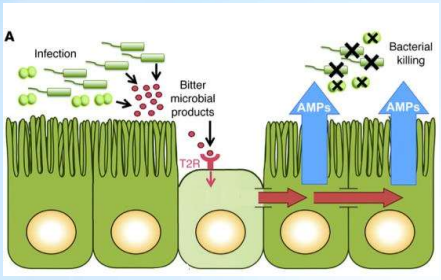
11

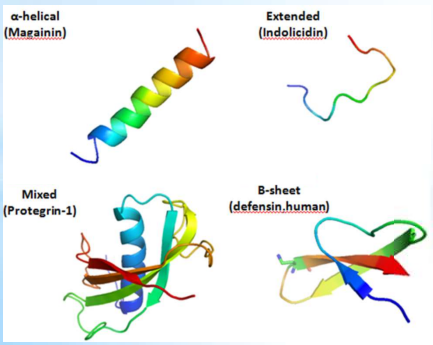


* **All mucous membranes (!)**
* Ancient, deeply conserved innate immune mechanism
* Unable to attack self
* "In-waiting" peptides known as AMPs (antimicrobial peptides) or host defense proteins (Reddy 2004)

*Immunologic peptides

12

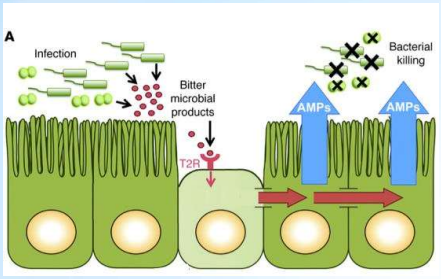


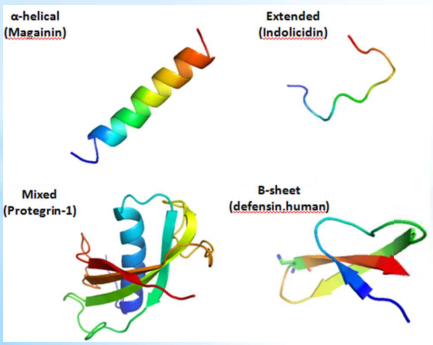


* AMPs secreted by bacteria to control competitors
* Triggered by T2R receptor stimulus in response to:
  * Bacterial endotoxins
  * Bacterial quorum-sensing molecules (AHL – acyl homoserine lactones)
  * Bitter tastants (lactones)
* (Carey 2016)

* Immunologic peptides

13

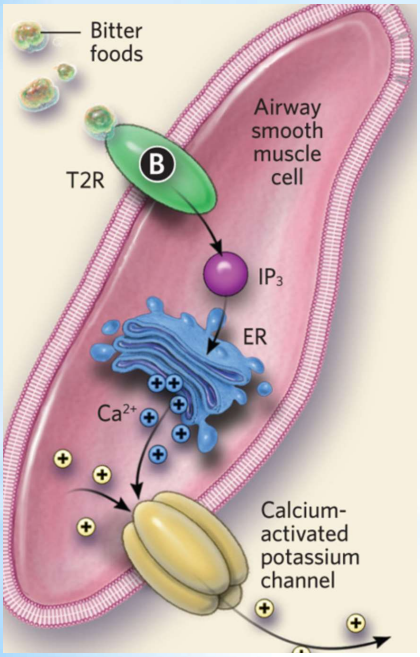




* Chronic infection in upper and lower airways:
  * Sinusitis (Lee/Cohen 2016)
* Effective against multi-drug-resistant bacteria:
  * MRSA, VRSA (Chung 2017)

* Immunologic peptides

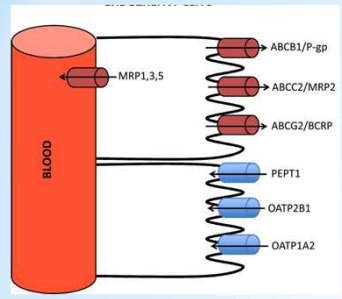
14



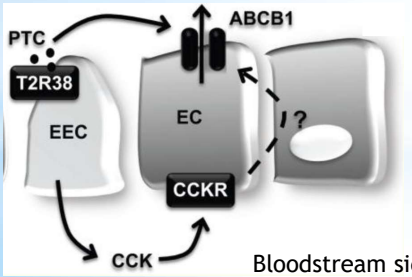
- Relaxant and bronchodilative (Deshpande 2010)
- Hyperpolarization through Ca-activated K channel
- Perhaps also NO activity increase (Carey 2017)
- Novel anti-asthma agents

Smooth muscle (airway)

15



Lumen side

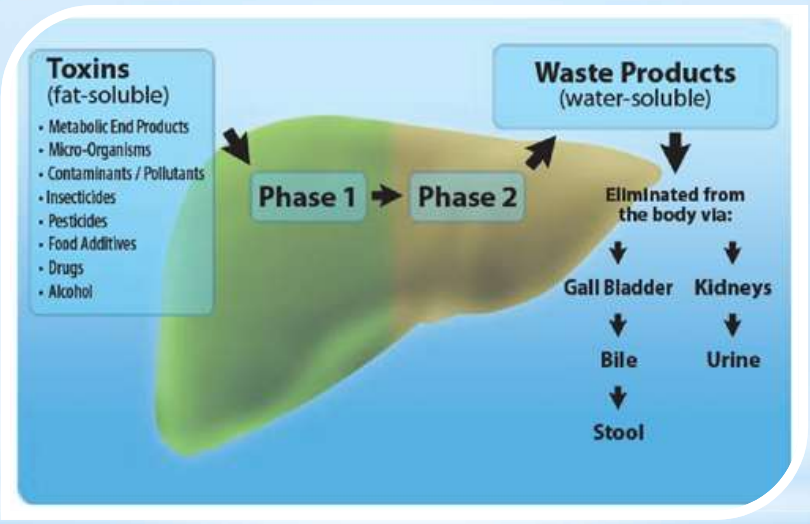


Bloodstream side

- Increased activity of ATP-binding-cassette B1 (ABCB1)
- Probably mediated by paracrine CCK effect from T2R-bearing enteroendocrine cells
- Pump toxins (bacteria, viruses) out of mucosal epithelial cells to prevent entry into blood

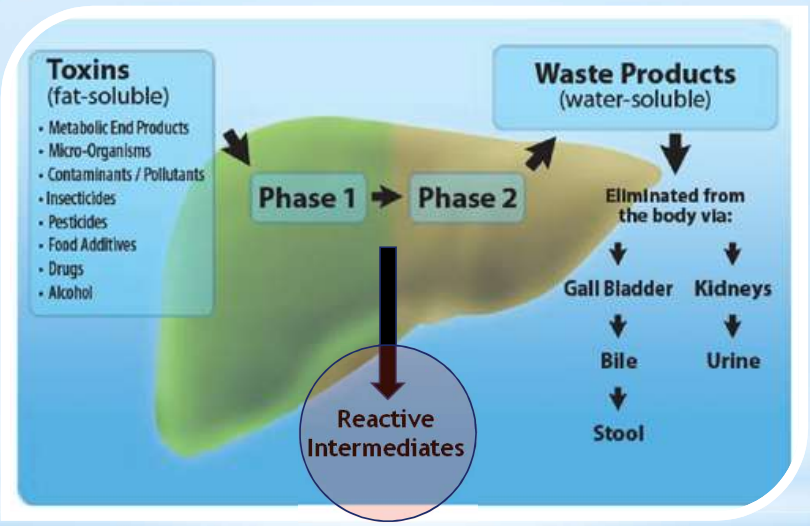
Efflux pumps

16



The Liver in hypersensitivity

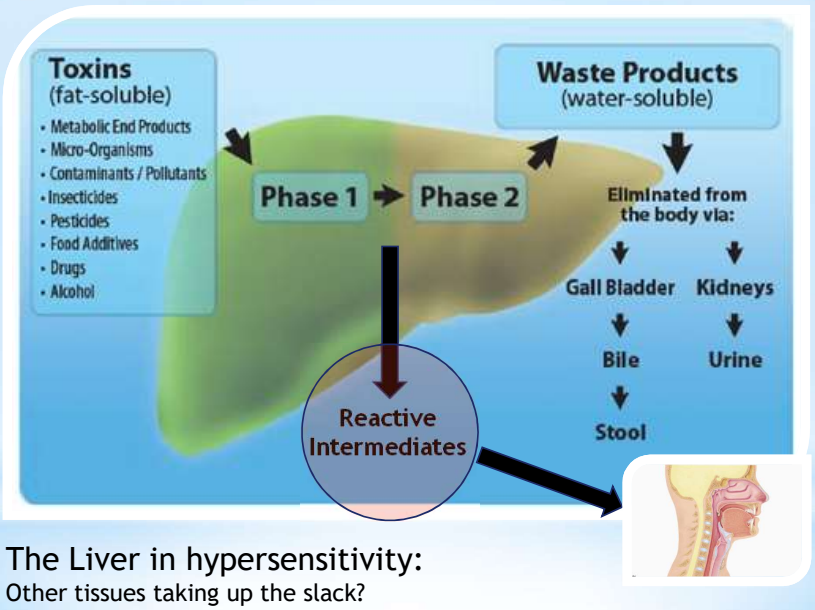
17



The Liver in hypersensitivity:
Contributing to "dirty blood"?

Bondy SC et al. "Contribution of hepatic cytochrome P450 systems to the generation of reactive oxygen species." (1994) Biochemical Pharmacology, 48 (1), pp. 155-159.

18



The Liver in hypersensitivity:

Other tissues taking up the slack?

Boyd et al (1983). "The Effect of Hepatic Metabolism on the Production and Toxicity of Reactive Metabolites in Extrahepatic Organs." Drug Metabolism Reviews 14 (1)

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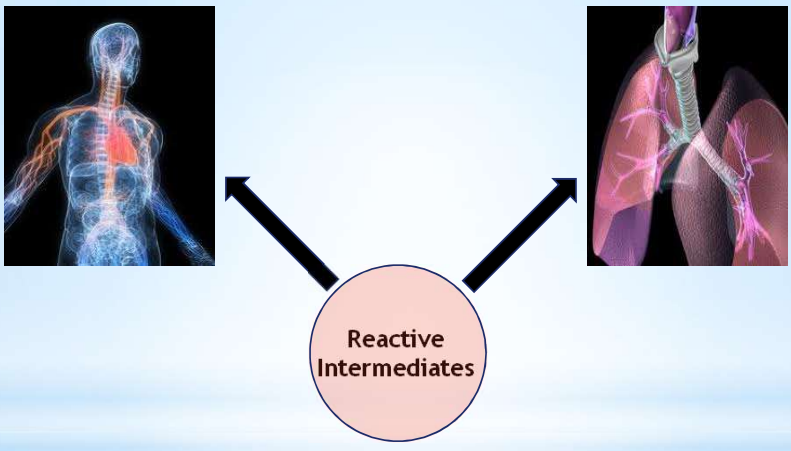

The Liver in hypersensitivity:

Links with systemic inflammation (Haukeland et al 2006)

Links with lung disease (Fallon et al 2003)

20

* Bitter tastants and liver metabolism:
  * T2R stimulation upregulates CCK (cholecystokinin) production and secretion
  * This relies on Phase 2 liver metabolism, particularly sulfonation, which is also increased
  * Specific bitter tastants (flavonoids, flavonolignans) can SLOW DOWN Phase 1, and at the same time SUPPORT Phase 2 (see: naringin, schisandrin, silymarin e.g.)
* Net result: more balanced Phase 1 - > Phase 2
* Fewer reactive intermediates
* "Bitters are cooling" – in this case, to the liver

Gamage, Niranjali, et al. "Human sulfotransferases and their role in chemical metabolism." *Toxicological sciences* 90.1 (2005): 5-22.

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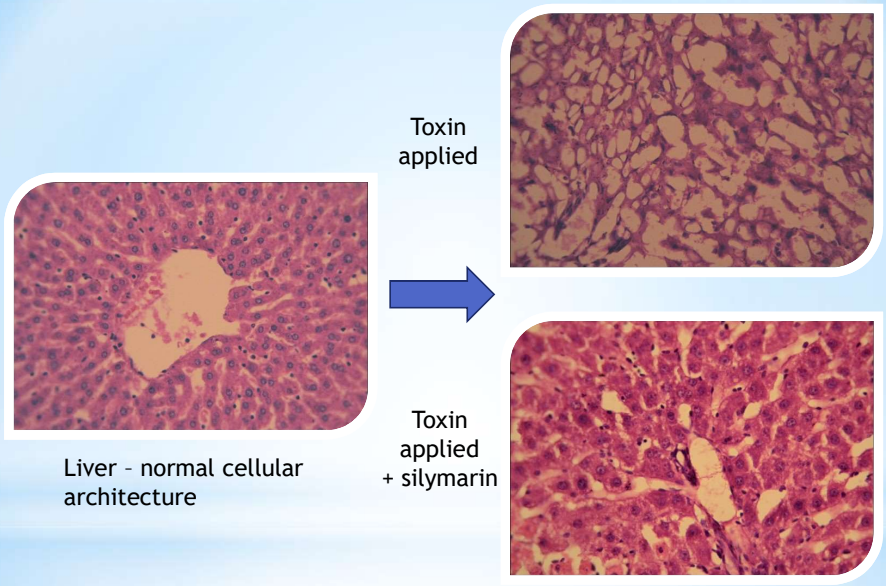

Saller R, Brignoli R, Melzer J, Meier R. "An updated systematic review with meta-analysis for the clinical evidence of silymarin." Forsch Komplementmed. 2008 Feb;15(1):9-20.

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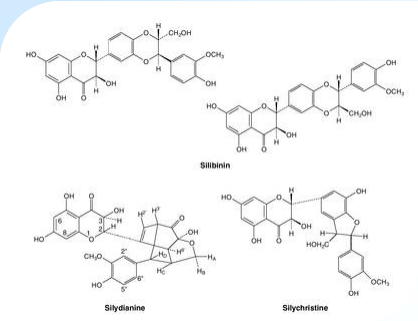

Saller R, Brignoli R, Melzer J, Meier R. "An updated systematic review with meta-analysis for the clinical evidence of silymarin." Forsch Komplementmed. 2008 Feb;15(1):9-20.

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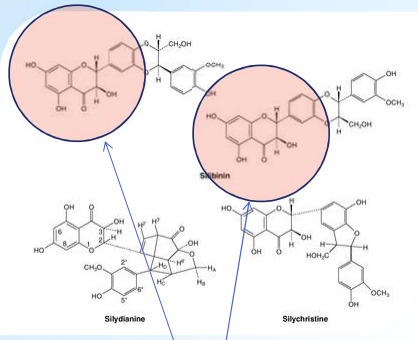

Silymarin is a flavo-lignan complex – flavonoid-related
Many different flavonoids have liver-enhancing and –protecting effects – especially when consumed as naturally-occurring cocktails

Egert S, Rimbach G. "Which sources of flavonoids: complex diets or dietary supplements?" Adv Nutr. 2011 Jan;2(1):8-14.

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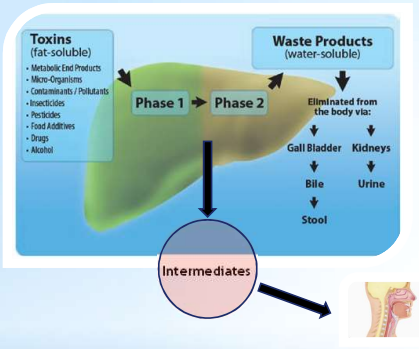


Bakhshaee M et al. "Effect of silymarin in the treatment of allergic rhinitis." Otolaryngol Head Neck Surg. 2011 Dec;145(6):904-9.

25

* Bitter tastants and gut permeability:
  * No direct evidence that intestinal T2R stimulation tightens gap junctions.
  * However, bitters support secretions across the whole GI tract, including digestive enzymes, hydrochloric acid, and bile.
  * Net result: modulation of bacterial populations, less antigenic (undigested material), less inflammation in the intestinal mucosa.
* "Bitters are cooling" – in this case, to the inflammation in the intestinal mucosa

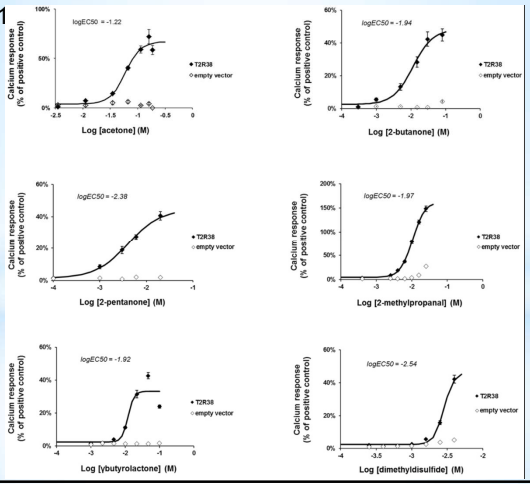
Gamage, Niranjali, et al. "Human sulfotransferases and their role in chemical metabolism." *Toxicological sciences* 90.1 (2005): 5-22.

26

Bacterial sensing:

- **Broadly tuned to bacterial metabolites** (see previous!)

Verbeurgt, Christophe, et al. "The human bitter taste receptor T2R38 is broadly tuned for bacterial compounds." *PloS one* 12.9 (2017): e01



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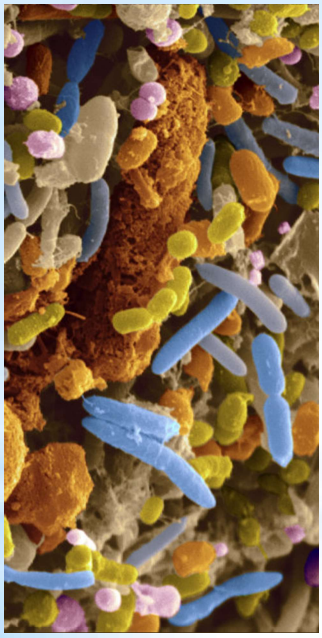

- Beneficial gut flora are some of the only microbes resistant to AMPs (!) (Cullen 2015)
- Gastric mucosal inflammation down-regulated via T2Rs (reduced immune cell activity) (Komarnytsky 2015)
- Net result: favor beneficial flora

Regulate microbial populations

28

1. Direct mucosal application with bitter tastants?
   - Tissue AMP stimulation via T2Rs – innate antimicrobial power
   - Tissue tonification / astringency

2. Liver :
   - Increased choleresis
   - Balancing of Phase 1 and Phase 2, fewer reactive intermediates

3. Intestinal mucosa :
   - Reduced inflammation from fewer undigested food components
   - Balanced microbial populations, favoring beneficial flora via AMPs

*Putting it all together

29

Bitters directly in the upper airway

- CHRONIC SINUSITIS / ALLERGY: NETI! 1 pint of water, ¼ tsp. salt, ¼ tsp. baking soda
- Water can be infusion of: Hydrastis (2g), Plantago (4-5g), Cinchona (2g)
- Tincture can be added: Hydrastis (1mL), Plantago (2mL), Cinchona (1mL)

Steep till cool, and strain infusions well. 1x/day, usually AM but some prefer before bed (esp. w/ allergies)



30

Bitters directly in the lower airway

- ASTHMA/ALLERGY. Challenging. Fine-mist atomizers are necessary; nebulizers (or direct inhalation of volatiles)
- NOTE: most essential oils (terpene content) are quite bitter. Direct inhalation of oils (Eucalyptus, e.g.) may be effective on reactive lower airways in part because of bitterness (+ terpenes are antispasmodic)
- Cloth, 3-4 drops essential oil, inhale deeply 5-6 times
- Steams with hot water and a towel

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Liver dysfunction

- Can be mild or severe, generally connected to inflammation
- General strategy: cholagogues, hepatoprotectants, elimination
  - Herbs rebalance hepatic metabolism (less intermediates)
  - Herbs improve toxin metabolism (less irritation)
- General administration: bitter tinctures
  - But also milk thistle seed, ground, as food

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Liver dysfunction

- Silybum marianum
  - 7-10 grams of whole, ground seed daily (mixed with grains)
  - If you must, 400mg daily of 80% silymarin
  - 3-5 ml of tincture three times daily before meals
- Flavonoid, flavo-lignan rich. Whole seed also has fat, fiber
- Especially for those with liver disease history
- Cooling

Bakhshaee M et al. "Effect of silymarin in the treatment of allergic rhinitis." Otolaryngol Head Neck Surg. 2011 Dec;145(6):904-9

33

Liver dysfunction

- Gentiana lutea
  - 1-2ml of tincture three times daily before meals
- Bitter iridoid rich
- Especially for those with digestive issues, food intolerances
- Traditional European allergy / asthma / sinusitis remedy
- Quite cooling

MB Antunes et al. "Complementary and Alternative Medicine in Rhinology." Rhinosinusitis, 2008

34

Mucosal irritation

- Solidago canadensis
  - 3ml of tincture three times daily
  - 5 grams daily in tea, taken throughout the day
- Flavonoid rich (esp. quercetin) – bitter and pungent
- Indicated in all allergic patterns, esp. if many mucous membranes
- Drying, cooling – also has decent digestive effects

35

Mucosal irritation

- Plantago lanceolata
  - 3ml of tincture three times daily
  - 5 grams daily in tea, taken throughout the day
- Tannin, flavonoid rich. Also bitter principles and soothing starches
- Indicated in variable allergic patterns: dry / swollen, e.g.
- Drying, cooling – but also soothing, moistening if necessary

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Mucosal irritation

- Euphrasia officinalis
  - 2 ml of tincture twice daily
  - Infusion made with 1tsp herb in 4oz water as eye wash
- Flavonoid, iridoid rich: anti-inflammatory and bitter
- Particularly for those with eye symptoms, digestive disturbance
- Cooling, drying

Stoss M et al. "Prospective cohort trial of Euphrasia single-dose eye drops in conjunctivitis." J Altern Complement Med. 2000 Dec;6(6):499-508.

37

- Bitters address dysfunction in the respiratory mucosa both directly and indirectly
  - Direct: antimicrobial effects via T2R-based AMP release
  - Direct: tissue tonification / astringency
  - Indirect: improved liver metabolism
  - Indirect: less inflammation and permeability in the GI mucosa
- Adjunct and follow-up considerations are necessary, for example:
  - Echinacea orally for secretory immune support (IgA via CB2 receptors)
  - Immunomodulation: Astragalus and/or medicinal mushrooms
  - Demulcency and soluble fiber: Linum, Malva, Ulmus, Symphytum
- …and some mucosae might want a little spice: Zingiber, Armoracia e.g.
- In the end, we have novel – and effective – strategies that harness our body's own defense and regulation mechanisms, address the symptoms, and leave us stronger

*Final Thoughts

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