



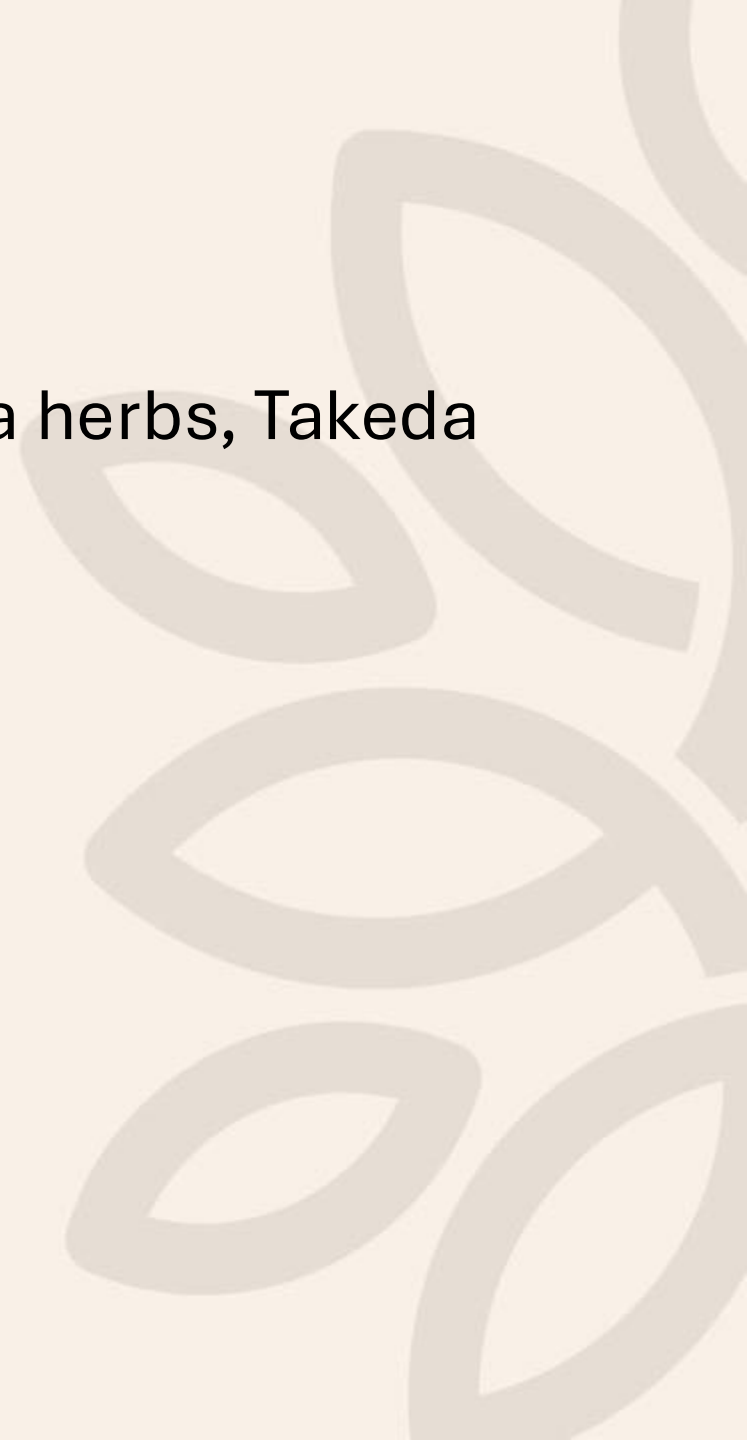
Integrating nutraceuticals into IBD Care: CurQD and Beyond

Nir Salomon
Sheba Medical Center, Tel-Aviv University, Israel

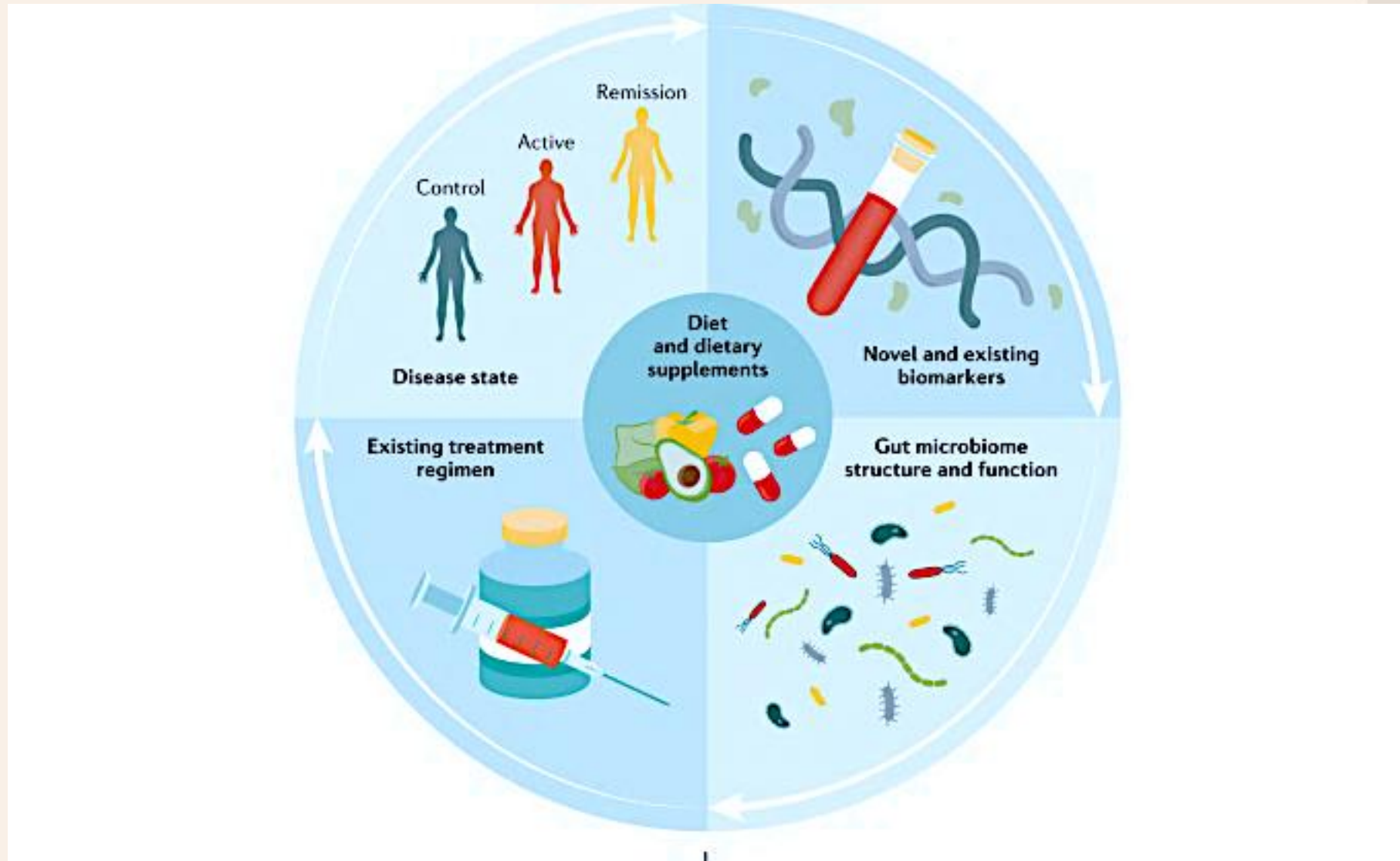


My disclosures

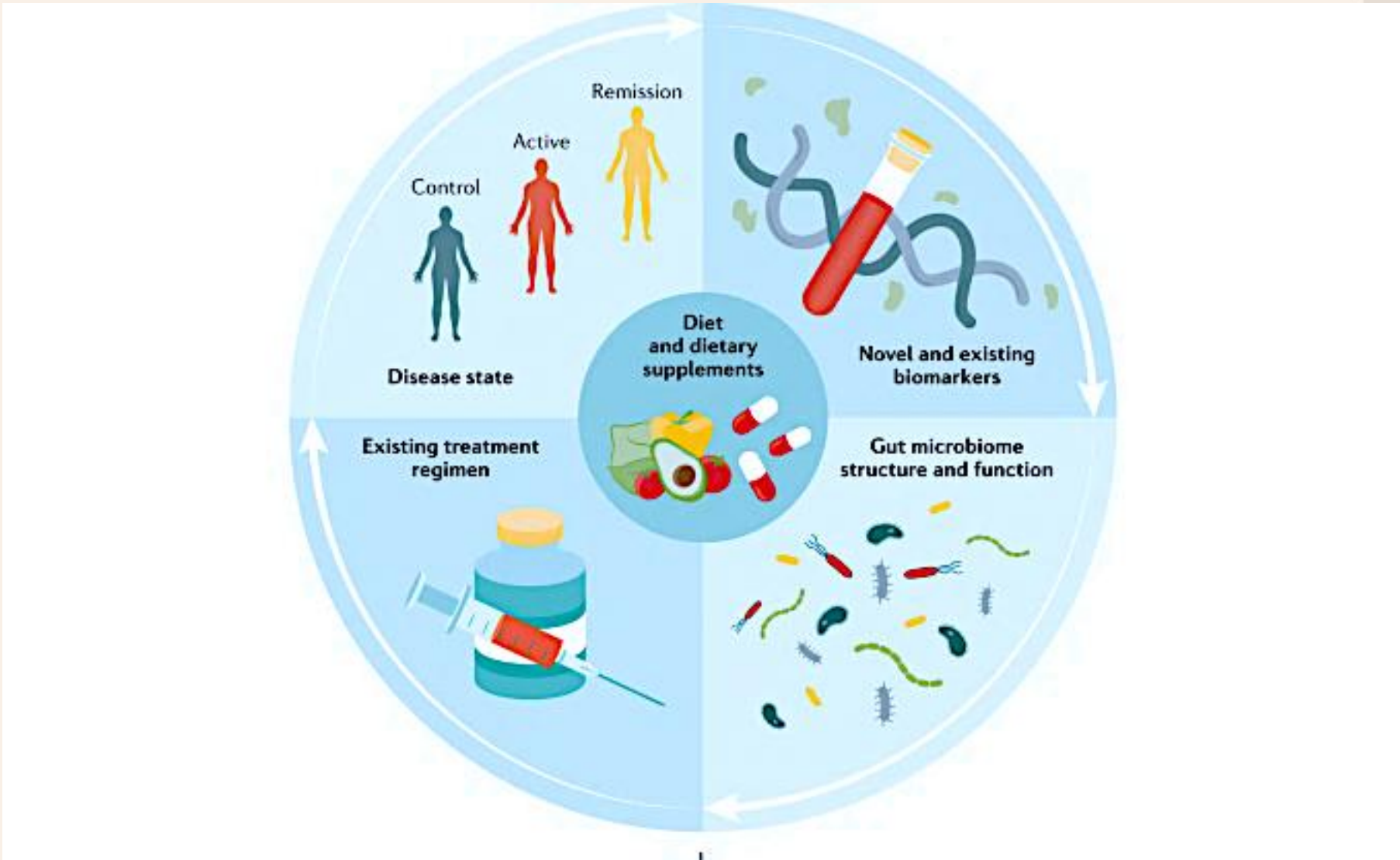
Received speaking fees from Janssen, Novartis, Bara herbs, Takeda
Hold an advisory and founding position at Evinature



Combination therapy does not need to be “advanced”: The Future



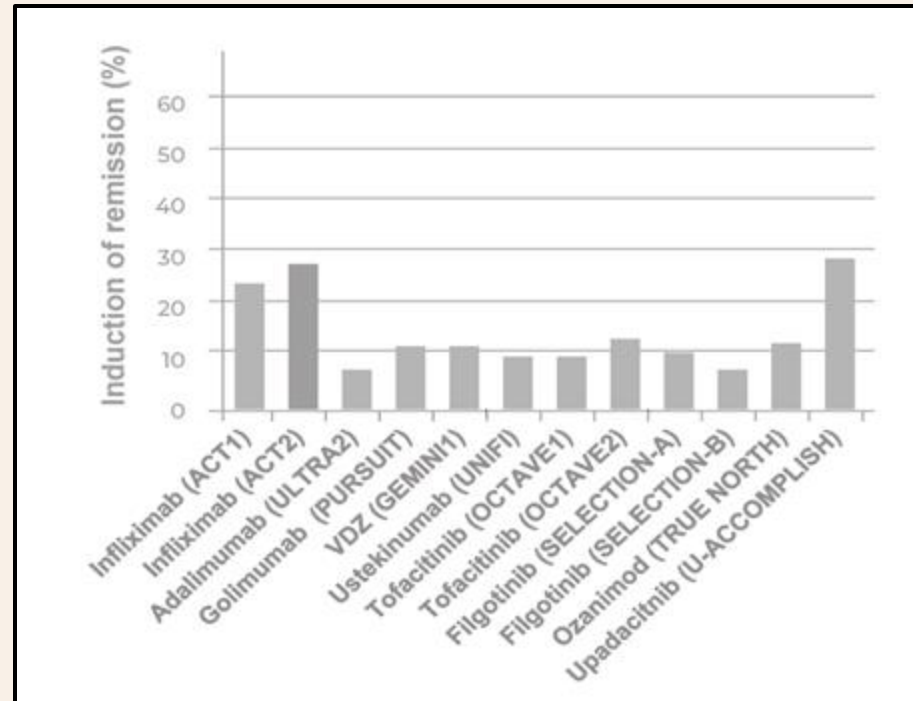
Combination therapy does not need to be “advanced”: ~~The Future~~ Present



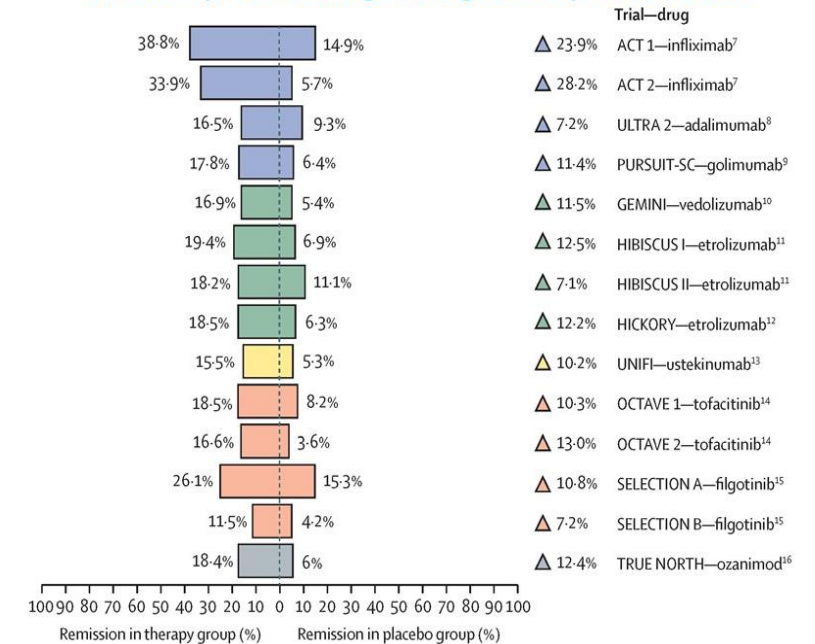
Wolter, M., Grant, E.T., Boudaud, M. *et al.* Leveraging diet to engineer the gut microbiome. *Nat Rev Gastroenterol Hepatol* **18**, 885–902 (2021).

Current IBD treatments are **still suboptimal**

New agents should be:
Oral
Accessible
Combinable
Safe MOA



The therapeutic ceiling in drug development in U.C.



What are we talking about?

nu·tra·ceu·ti·cal

A food possessing medicinal benefits

(Ginseng, Echinacea, Folic acid, Glucosamine...)

So what's the problem?

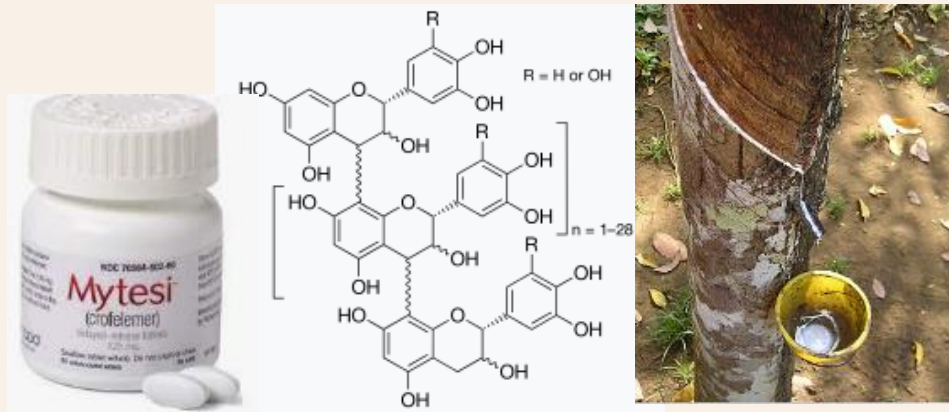
Nutraceuticals can't be claimed to treat disease

(Dietary Supplement Health and Education Act of 1994)

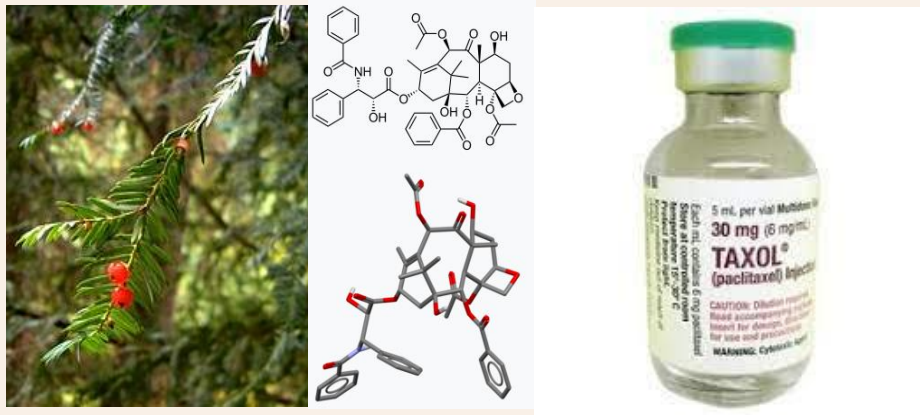
It's old news...

Therapeutic molecules identified from herbal medicine

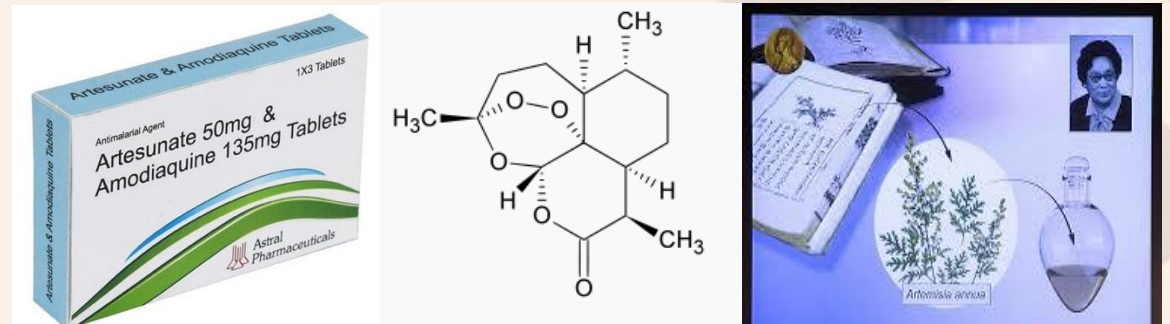
Crofelemer extracted from South American tree *Croton lechleri* ("Dragon blood")



Paclitaxel extracted from the Pacific yew tree, used by native Americans traditional medicine



Artemisinin, extracted from the plant *Artemisia annua* (sweet wormwood), a Chinese traditional medicine herb



The image is a poster celebrating Tu Youyou's 2015 Nobel Prize in Physiology or Medicine. The text reads: "First Chinese Woman To Win Nobel Medicine Prize 2015: Victory for Traditional Chinese Medicine". The central text says "2015 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE". A portrait of Tu Youyou is on the right, with her name "Tu Youyou" below it. The bottom left features the Qvitality logo and the tagline "Natural Health for Men at Midlife". The bottom right has the website "http://www.qvitality.com".

Problem #1:

Real life use of integrative medicine in IBD

- **Over 50% of IBD patients use integrative medicines**
- **Diet & Integrative medicine are among the most sought topics by IBD patients on social media**
- **Over 70% of patients don't inform their physicians about CM use**



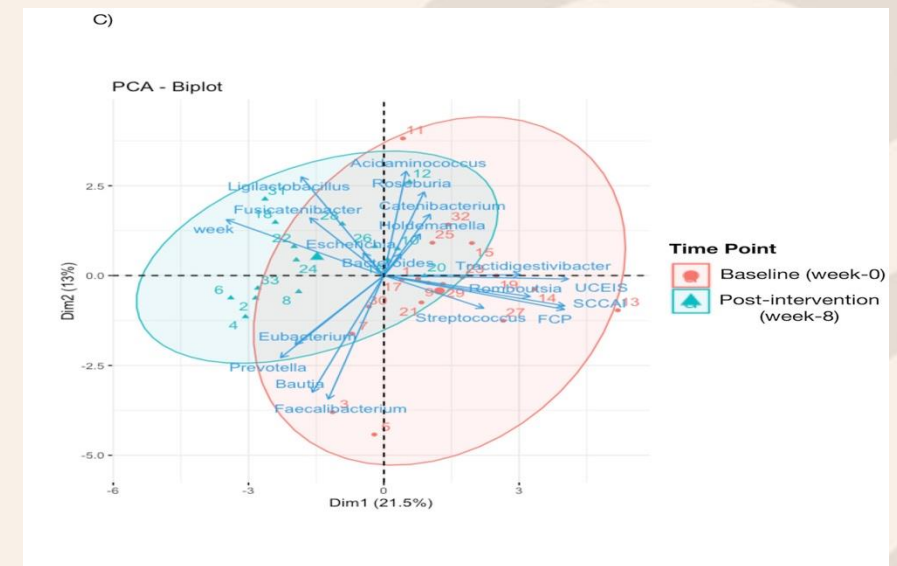
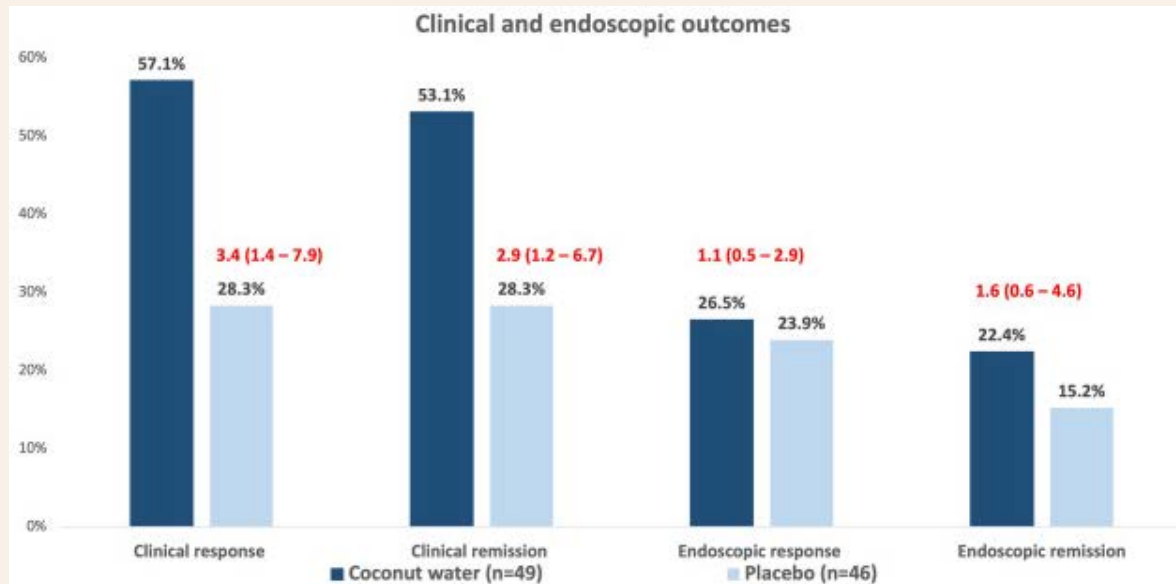
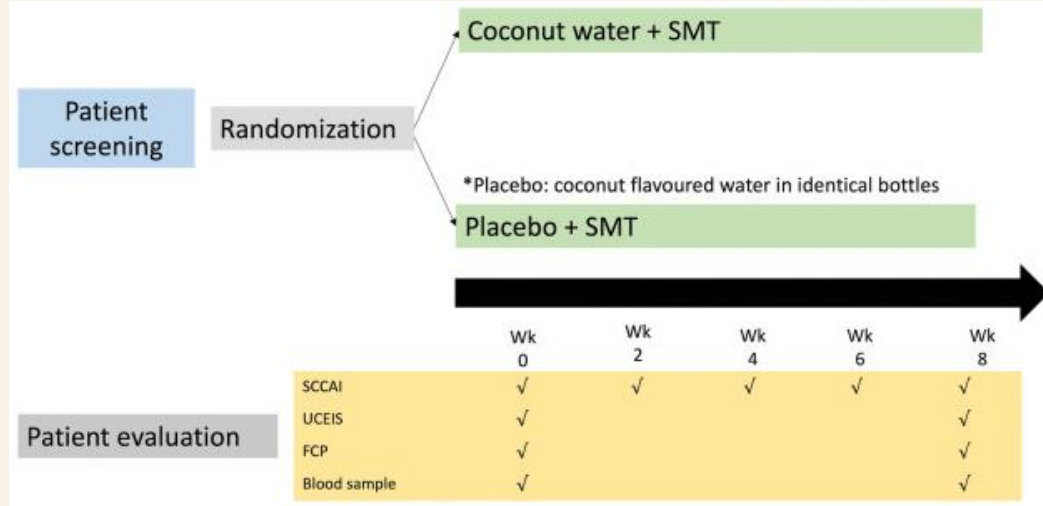
Problem #2:

Real life use of integrative medicine in IBD

- **Inconsistent manufacturing quality**
- **No standardization of compounds**
- **No authoritative guidance**



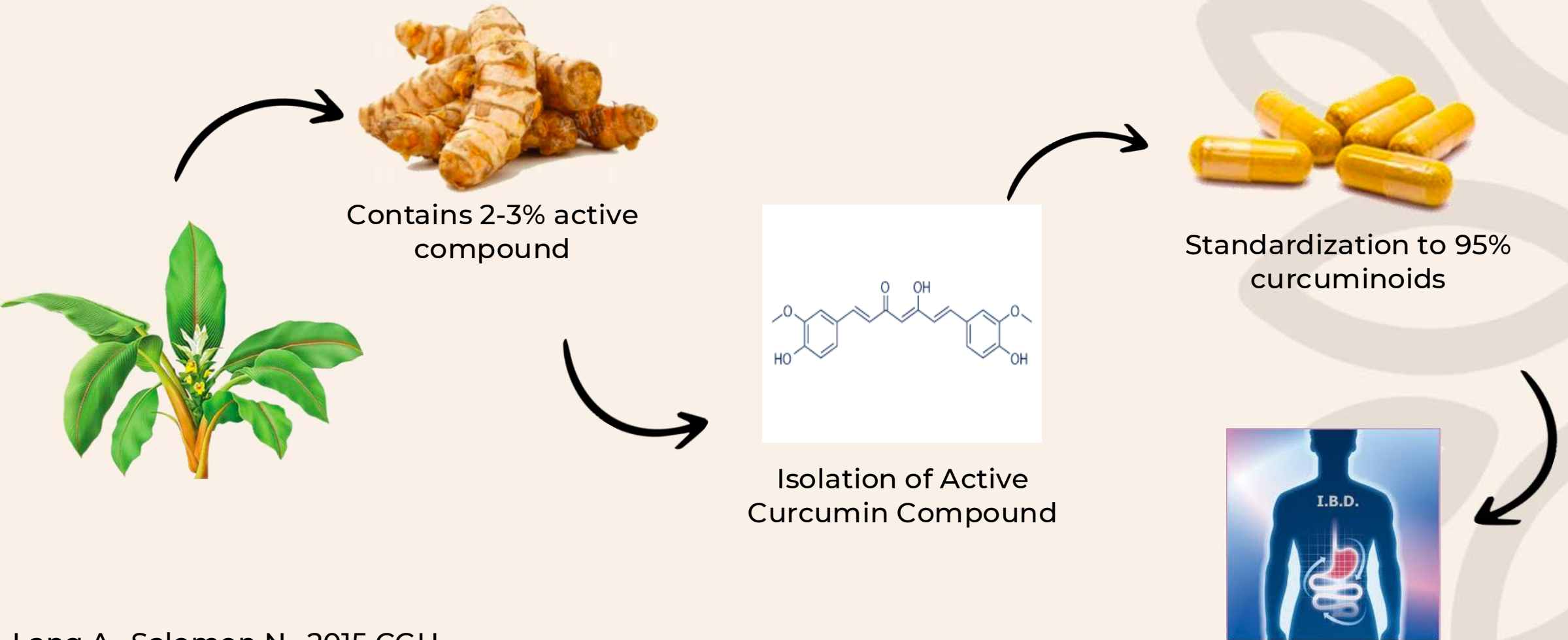
Coconut water induces clinical remission in mild to moderate active UC: Double-blind Placebo-controlled Trial



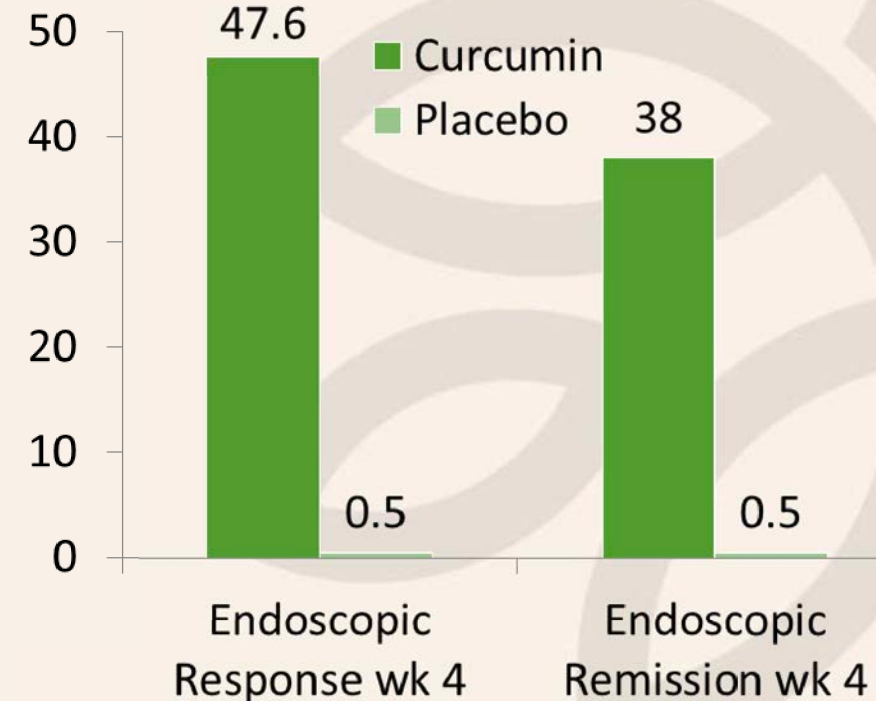
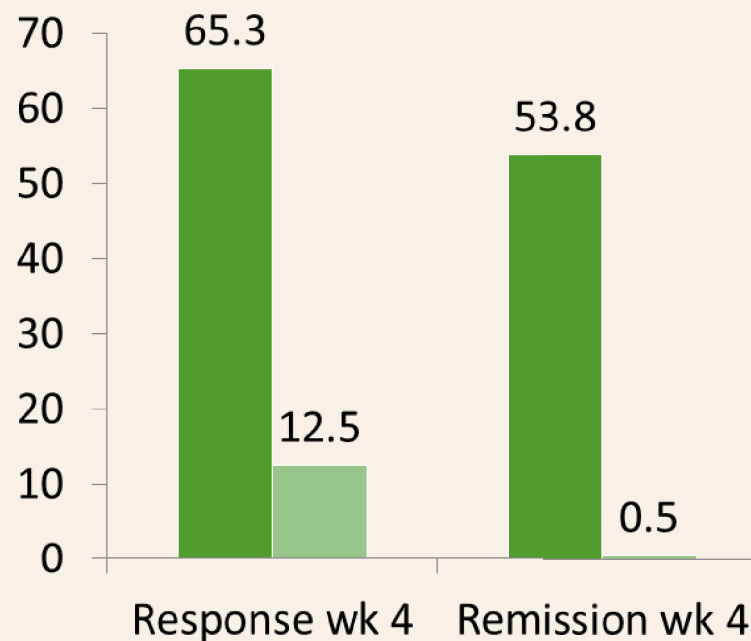
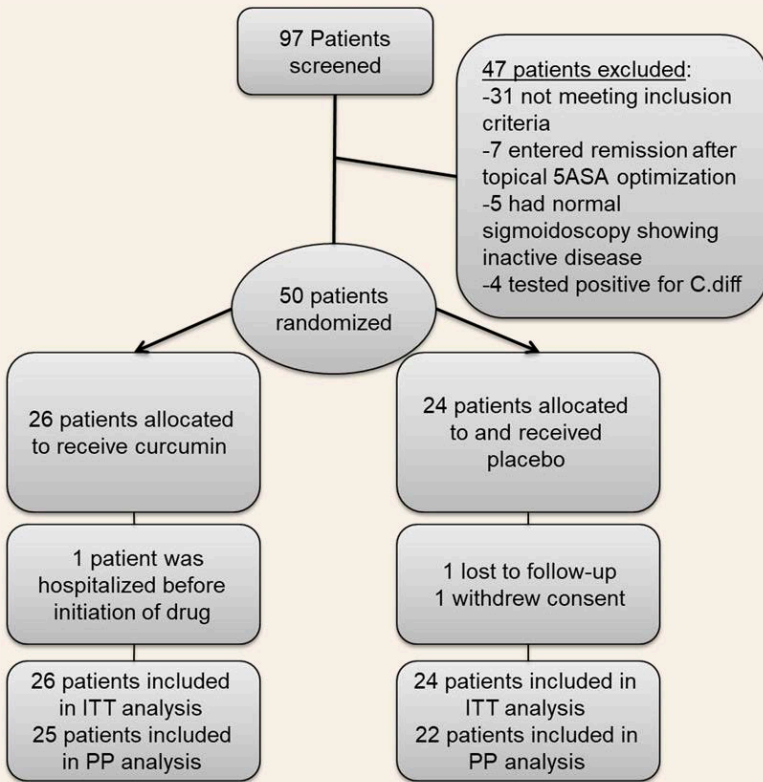
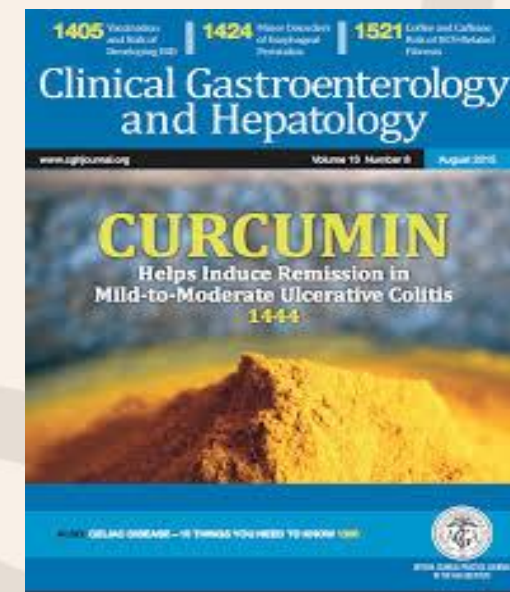
CW induced shift in microbial composition

A nutraceutical development process

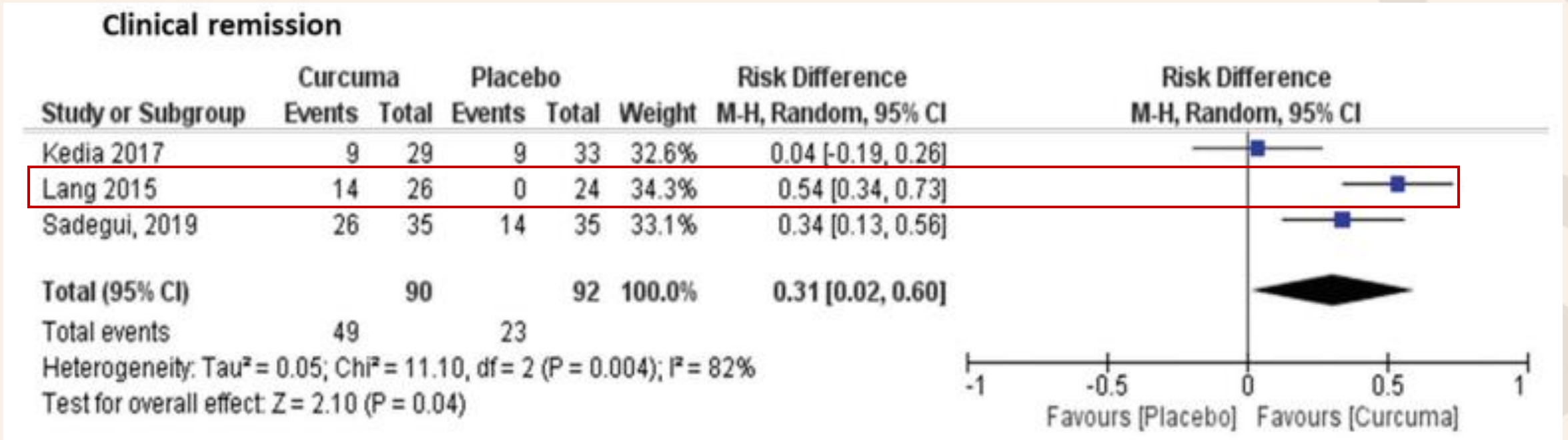
Turning Turmeric into a Gut-Directed Curcumin Formulation



Curcumin add-on to maximal 5ASA in mild-mod UC: A double-blind randomized placebo-controlled trial



Curcumin in mild-moderate ulcerative colitis



Goulart, Expert Review Gastro 2020

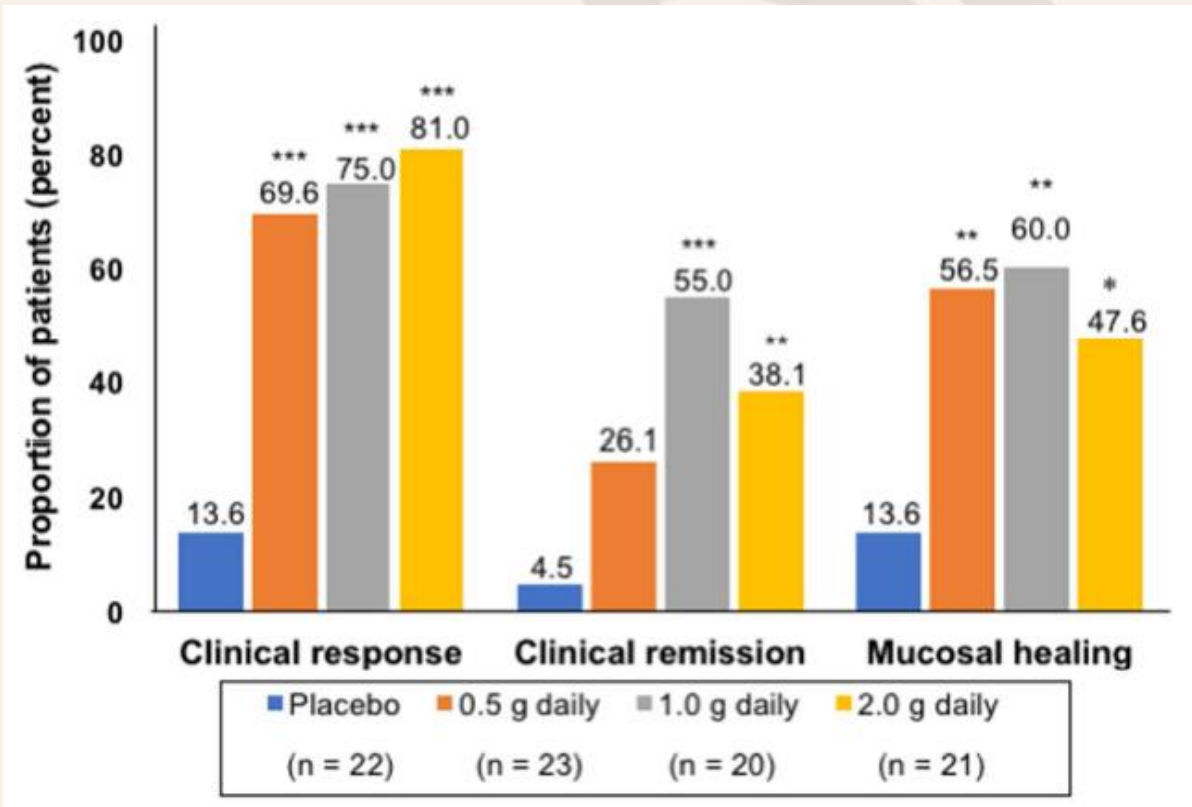
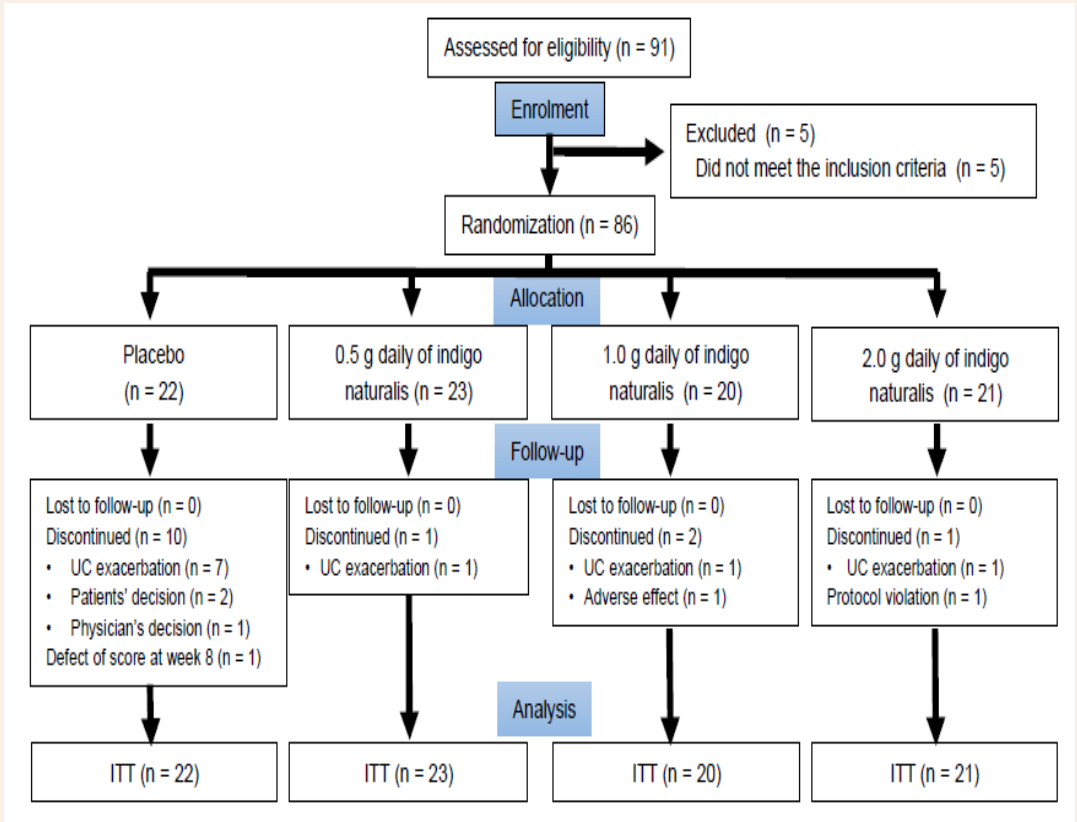
Current Practice Position 3.2

Curcumin as a complementary therapy to 5-aminosalicylic acid (5-ASA) may be effective in inducing remission in mild-to-moderately active ulcerative colitis (UC).

Torres J, ECCO Topical Review on Complementary Medicine in IBD, *J Crohn Colitis* 2019

Qing Dai (QD) in active UC

A double-edged sword



Qing Dai (QD) in active UC

A double-edged sword

Adverse events in patients with ulcerative colitis treated with indigo naturalis: a Japanese nationwide survey

Naganuma, 2019. Journal of Gastroenterology

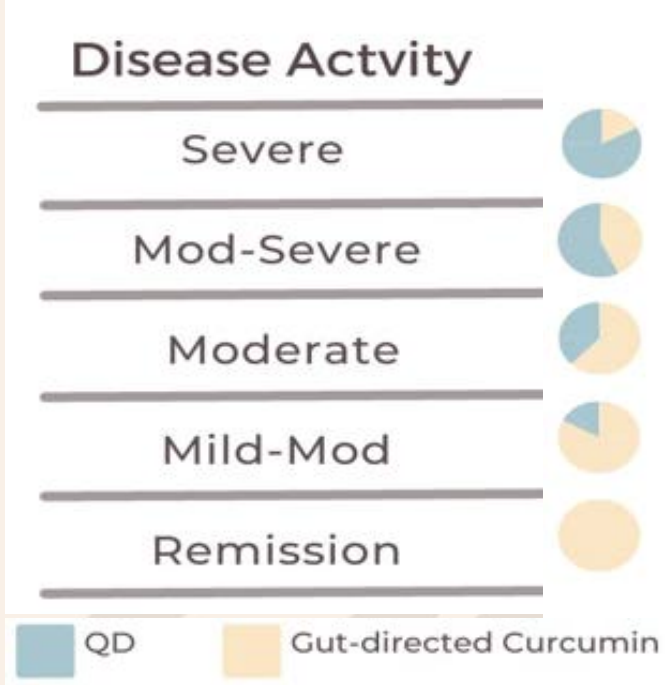
- Modestly elevated liver enzymes : 5%
- Transient headaches : 3%
- Rare pulmonary arterial hypertension (with prolonged high doses)
- Rare allergic right-sided ischemic colitis/intussusception

All AEs were reversible when Qing Dai stopped



Curcumin QingDai combination (CurQD)

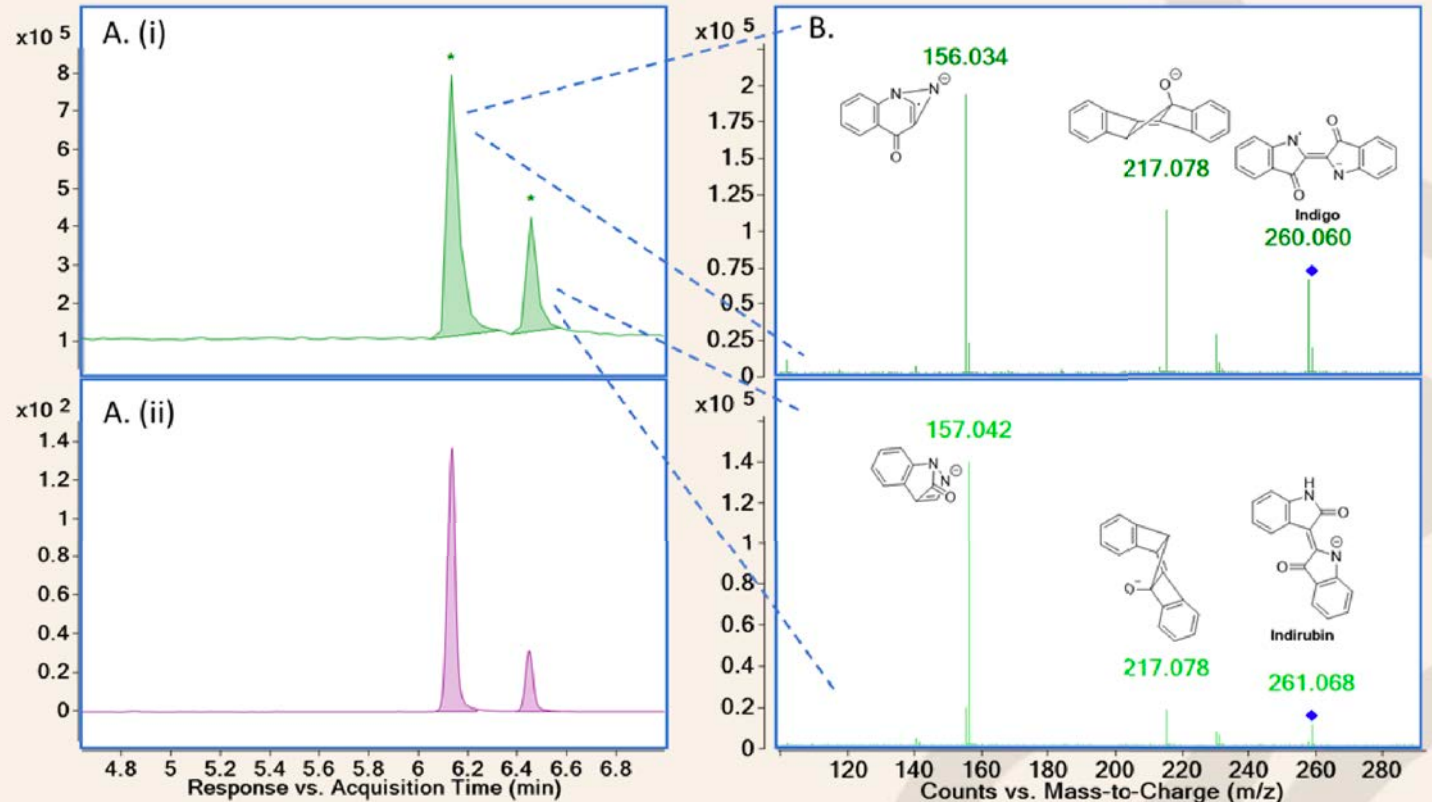
A combination of two evidence-based nutraceuticals



“Medical-grade” standardization

Determining effective and safe levels of active molecular moieties
Indigo and ***Indirubin*** in ***CurQD***

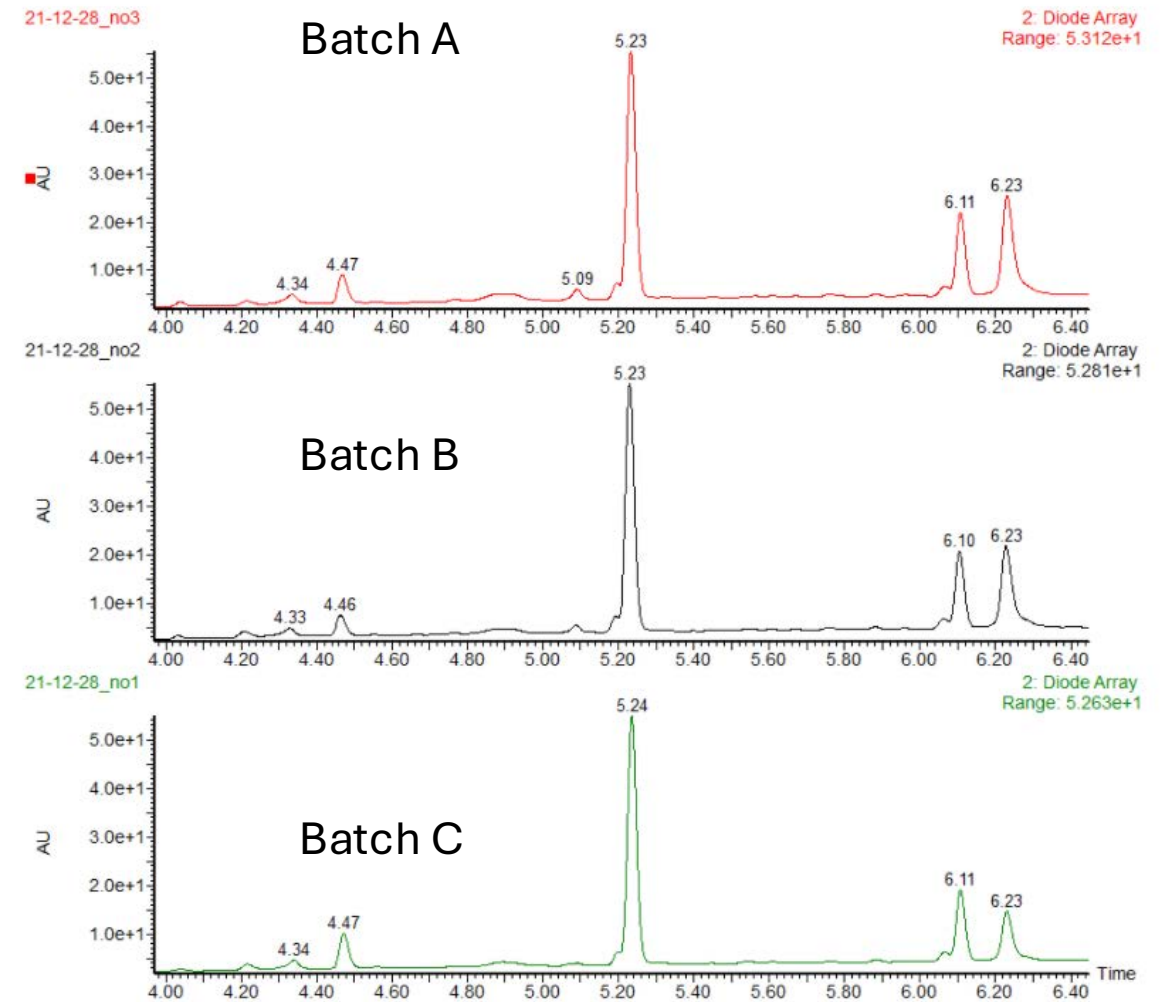
LC-MS/MS analysis:



A. (i) Extracted ion chromatogram (EIC) of the deprotonated precursor ions indigo (260.060 m/z, [M-H]⁻) and radical anion indirubin (261.068 m/z, [M]^{•-}). The x-axis represents retention time (min), and the y-axis represents signal intensity. A. (ii) UV chromatogram (detection wavelength, 611 nm) of indigo and indirubin. B. Fragmentation mass spectra by collision-induced dissociation of indigo and indirubin. Precursor ions are designated as ♦. The x-axis represents mass to charge (m/z), and the y-axis represents signal intensity. Putative assignments of characteristic fragment ions are shown.

“Medical-grade” standardization

No botanical similarity can be assumed
(No “botani-similars” just yet...)



CurQD add-on therapy in refractory UC

A Multi-Center Retrospective Study

8-12 weeks induction in moderate-severe UC patients.

At initiation:

51% failing 5ASA

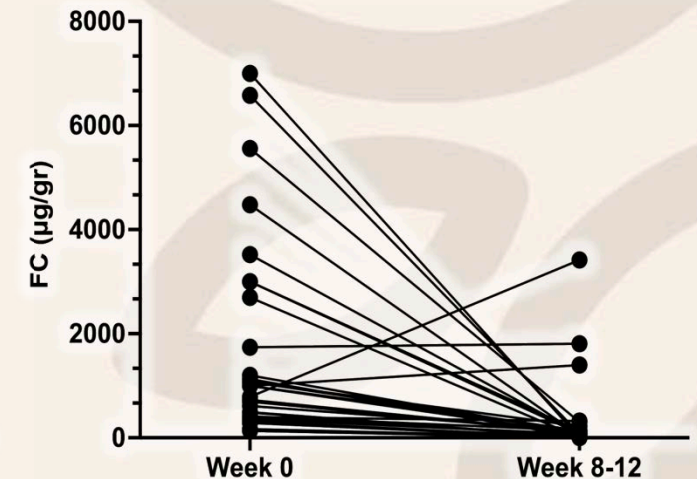
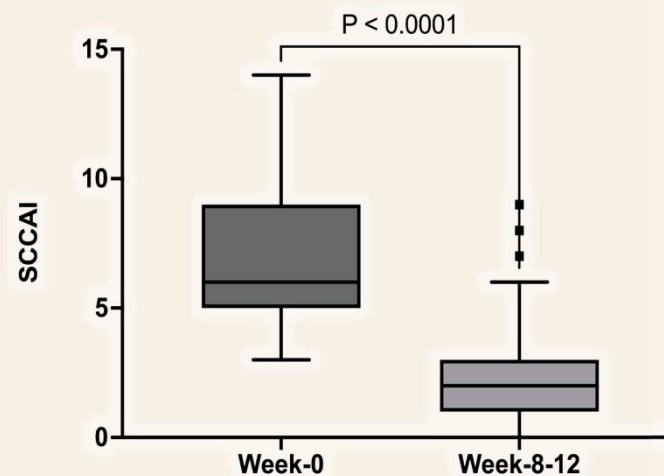
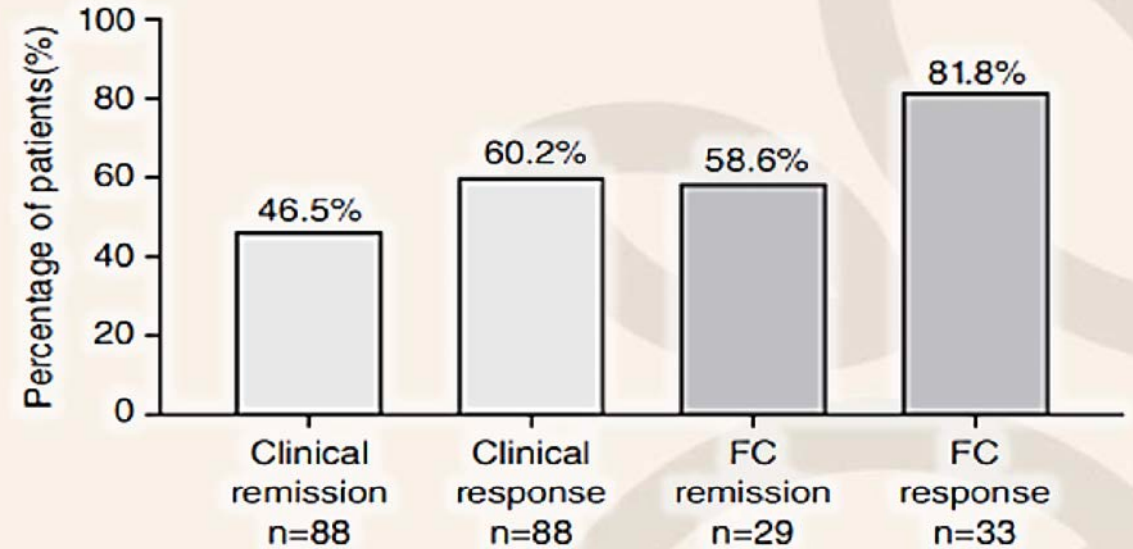
49% failing a biologic

Prior:

39.2% failed ≥ 2 biologics /small molecule with

Significant clinical and biomarker response

Similar response rate in bio-experienced patients



CurQD add-on therapy in refractory UC

A Randomize, Placebo-controlled Trial

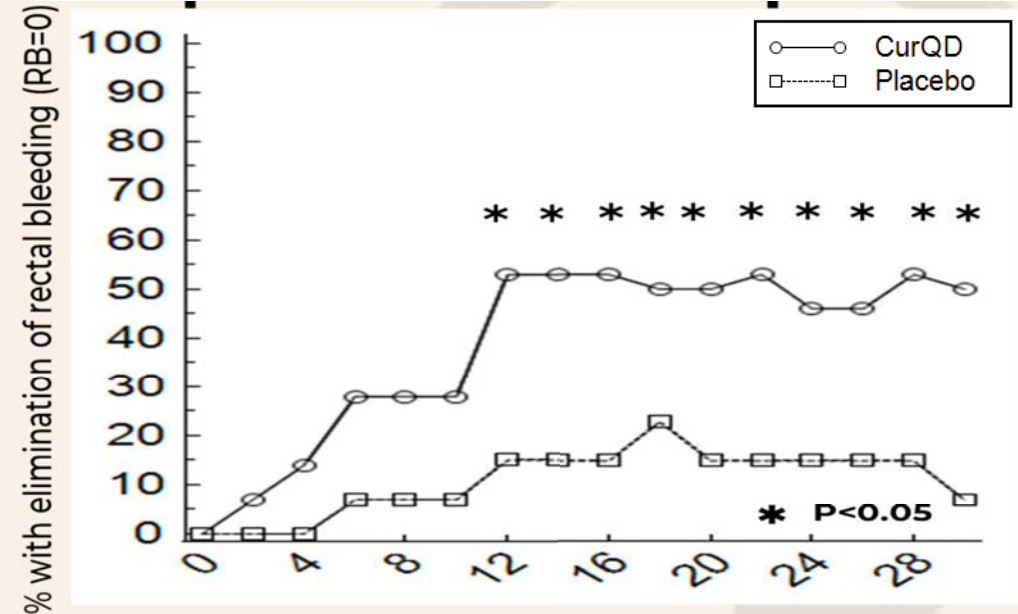
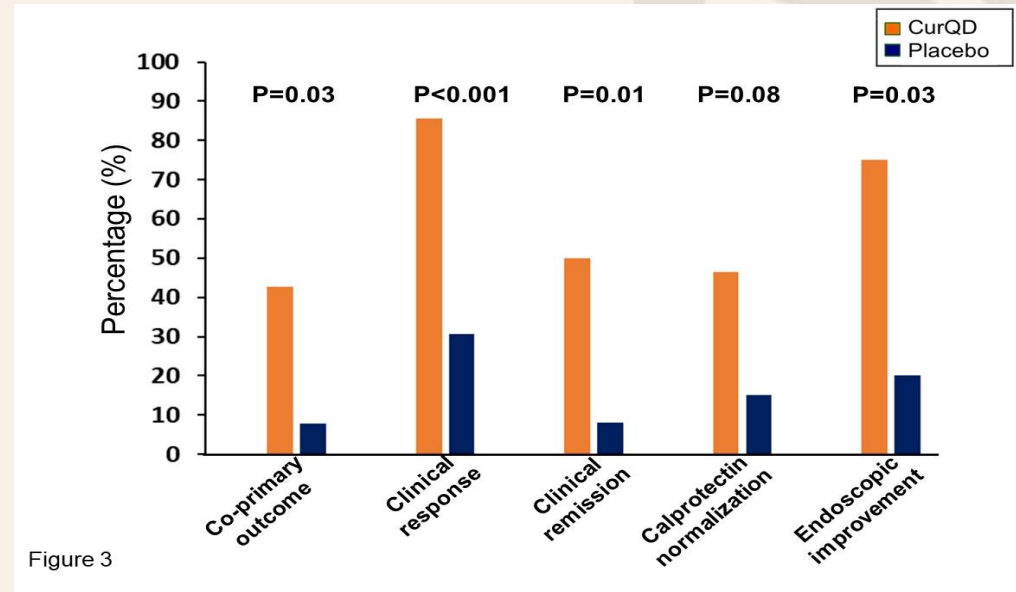
8 weeks induction in moderate-severe UC patients.

At initiation:

52% failing 5ASA

48% failing a biologic

CurQD superior to placebo in inducing clinical and endoscopic remission



Adverse events were comparable

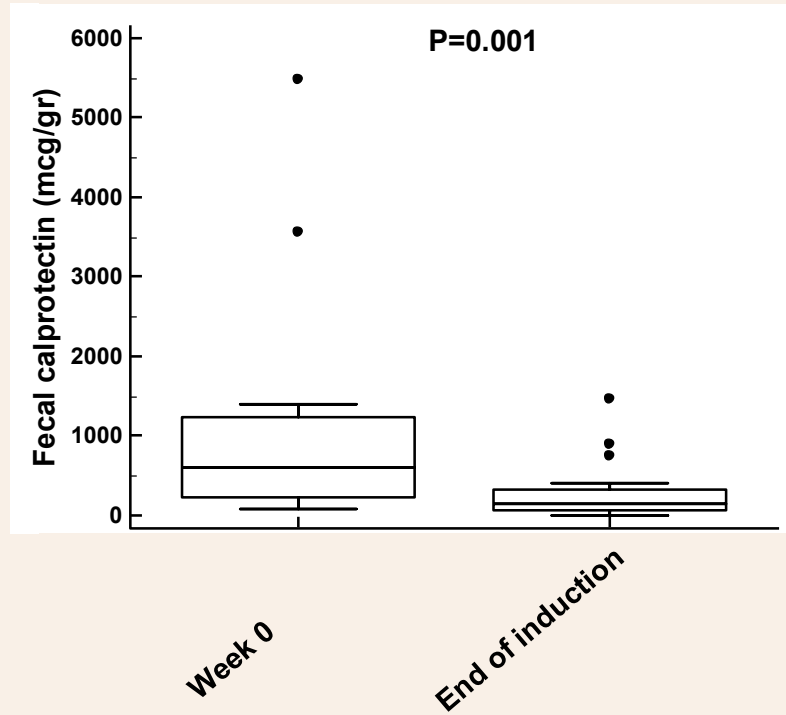
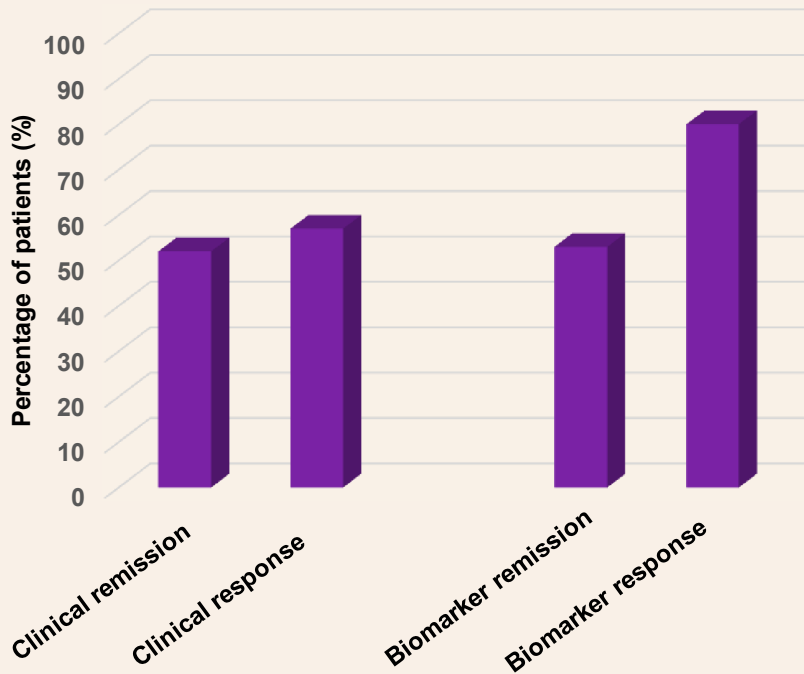
	CurQD (n=45)	Placebo (n=13)
Infection	0 (0%)	1 (7.7%)[§]
Nausea	2 (4.4%)	0 (0%)
Fatigue	2 (4.4%)	1 (7.7%)
Headache	11 (24.4%)	2 (15.4%)
Fever	2 (4.4%)	0 (0%)
Myalgia	1 (2.2%)	0 (0%)
Liver enzyme elevation	4 (8.9%)	1 (7.7%)
Worsening of colitis	5 (11.1%)	6 (46.1%)
AEs requiring discontinuation	6 (13.3%)	6 (46.1%)
Discontinue for Non-colitis AEs	1 (2.2%)	0 (0%)

No PAH with before-after echocardiography

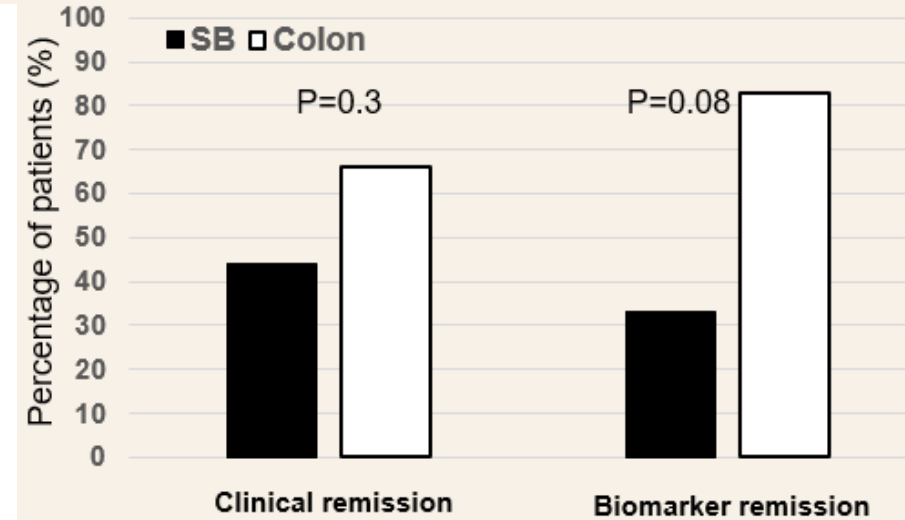
Efficacy of CurQD for Active CD

A Real-world retrospective cohort study (n=25)

Clinical and biomarker outcomes

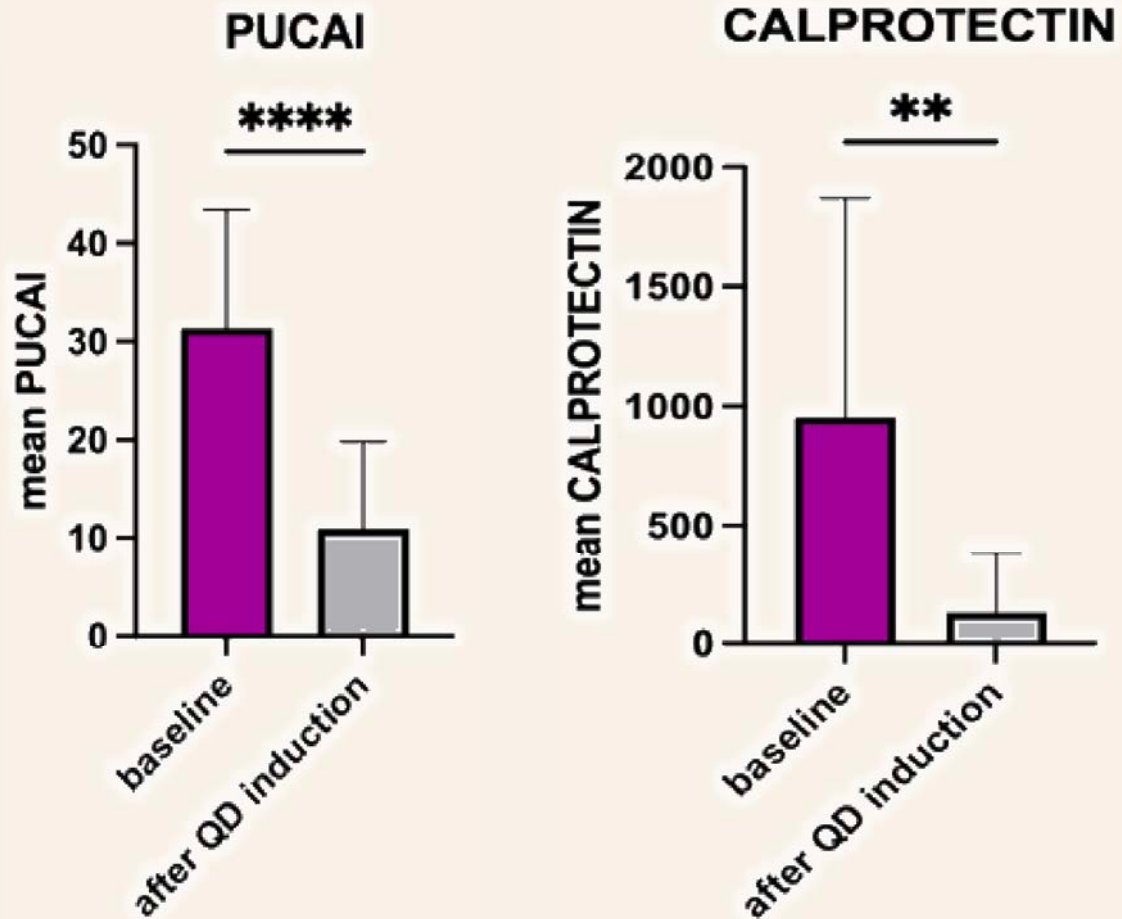


Colonic & ileocolonic versus SB disease



Pediatric data

In multi-center pediatric active UC, CurQD showed 70% clinical and biomarker response
Including patients failing biologics



Retrospective real-world pediatric cohort (Children Hospital, Los-Angeles) with intestinal US response to CurQD

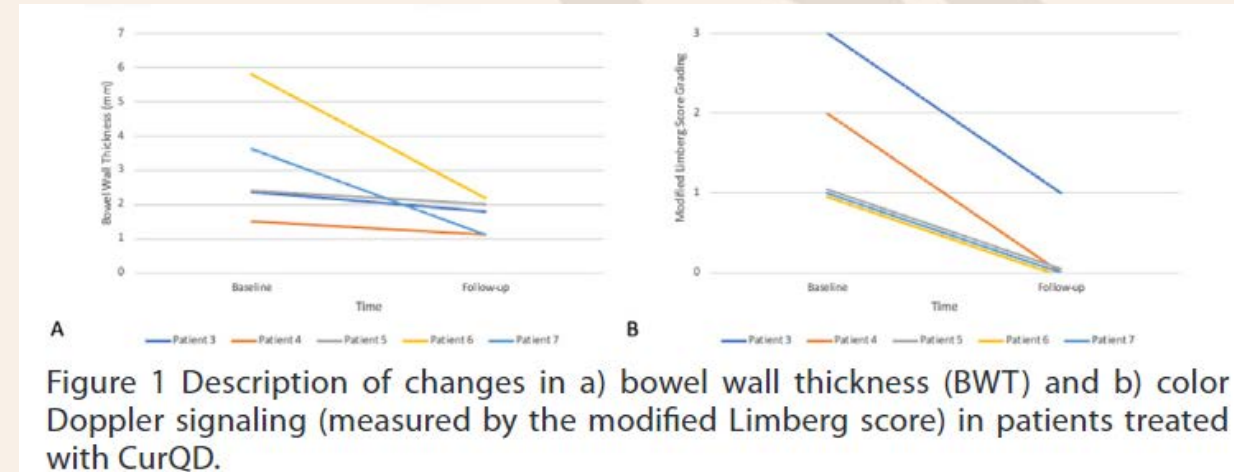
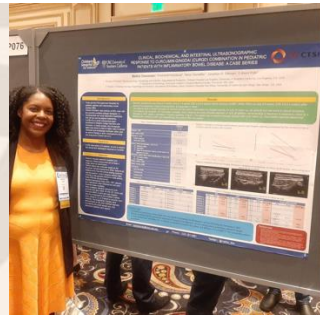


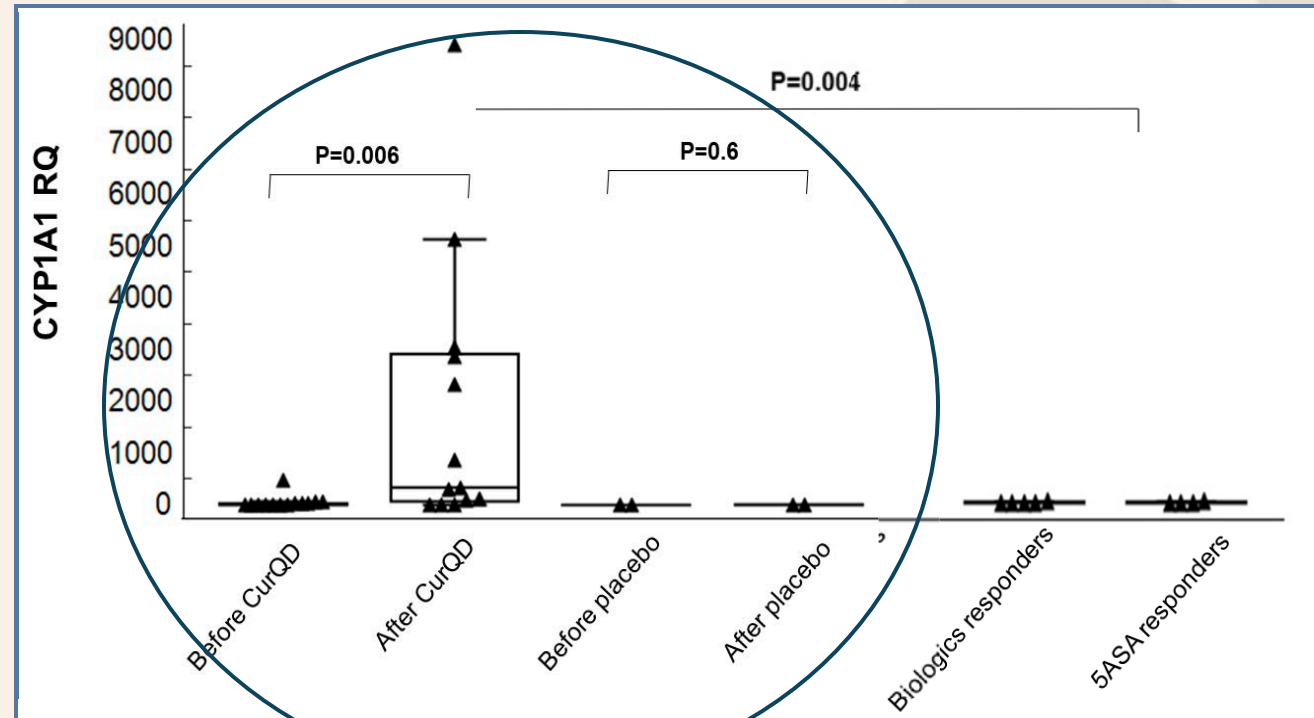
Figure 1 Description of changes in a) bowel wall thickness (BWT) and b) color Doppler signaling (measured by the modified Limberg score) in patients treated with CurQD.



CurQD as a Aryl hydrocarbon receptor (AhR) agonist

A master regulator of immune-mediated diseases

CurQD induces AhR activation in the intestinal mucosa, which is not seen after placebo,

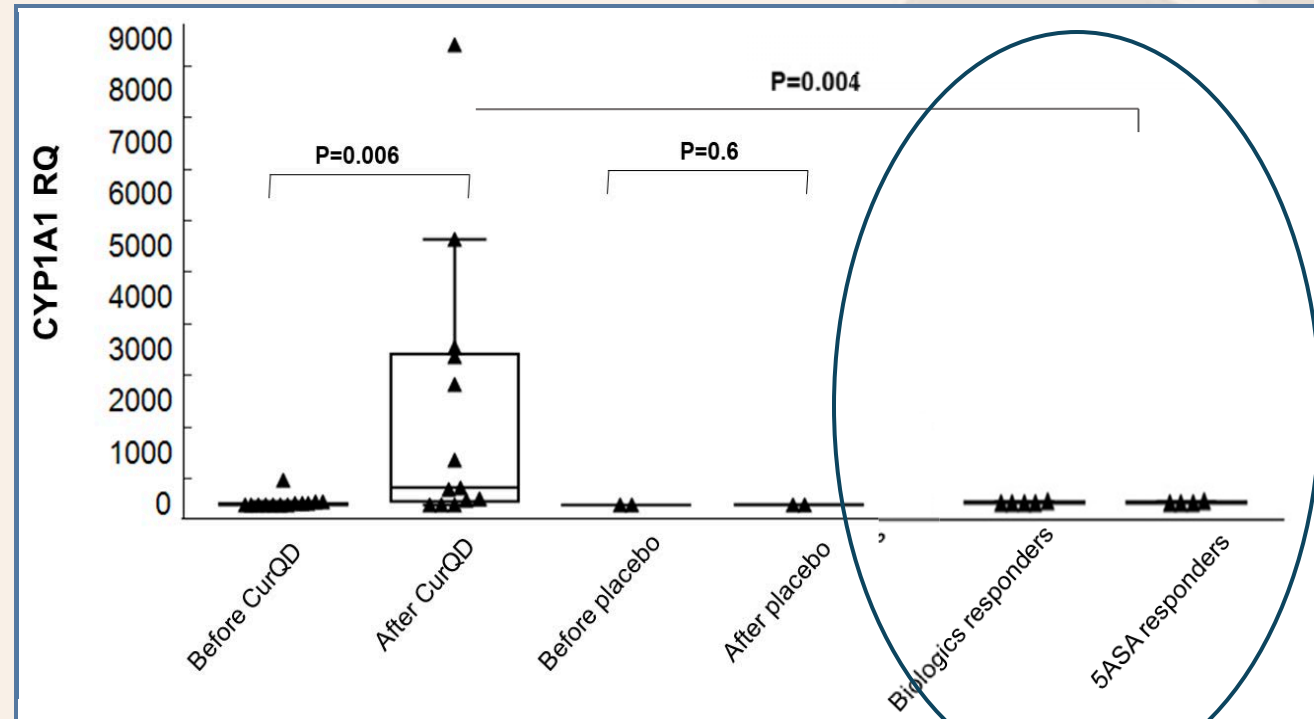


Rectal mucosal biopsies RNA expression of Cyp1A1 in UC patients before and after treatment with CurQD, and compared with patients responding to other agents (biologics or 5ASA)

CurQD as a Aryl hydrocarbon receptor (AhR) agonist

A master regulator of immune-mediated diseases

CurQD induces AhR activation in the intestinal mucosa, which is not seen after placebo, nor after IFX/VDZ or 5ASA

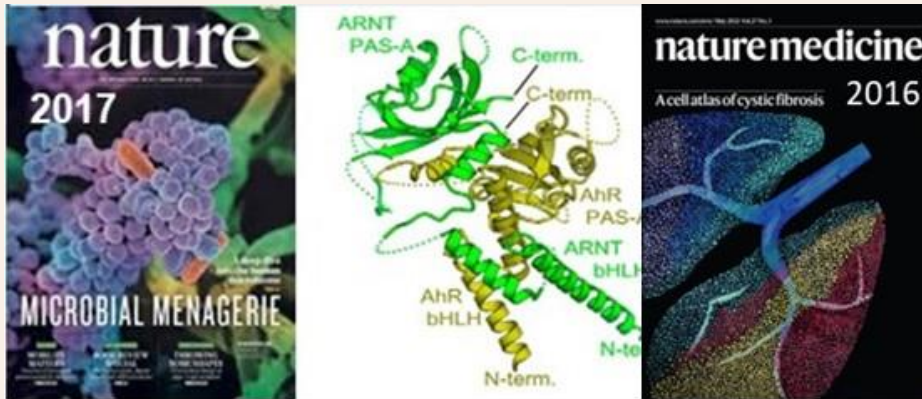


Rectal mucosal biopsies RNA expression of Cyp1A1 in UC patients before and after treatment with CurQD, and compared with patients responding to other agents (biologics or 5ASA)

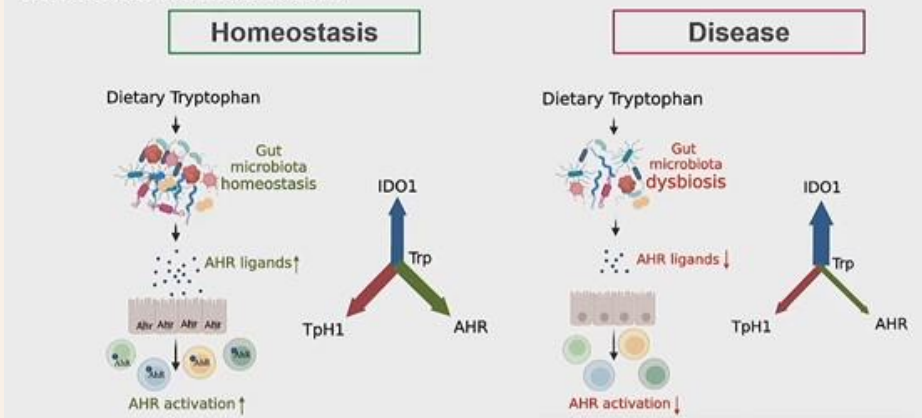
CurQD as a Aryl hydrocarbon receptor (AhR) agonist

A master regulator of immune-mediated diseases

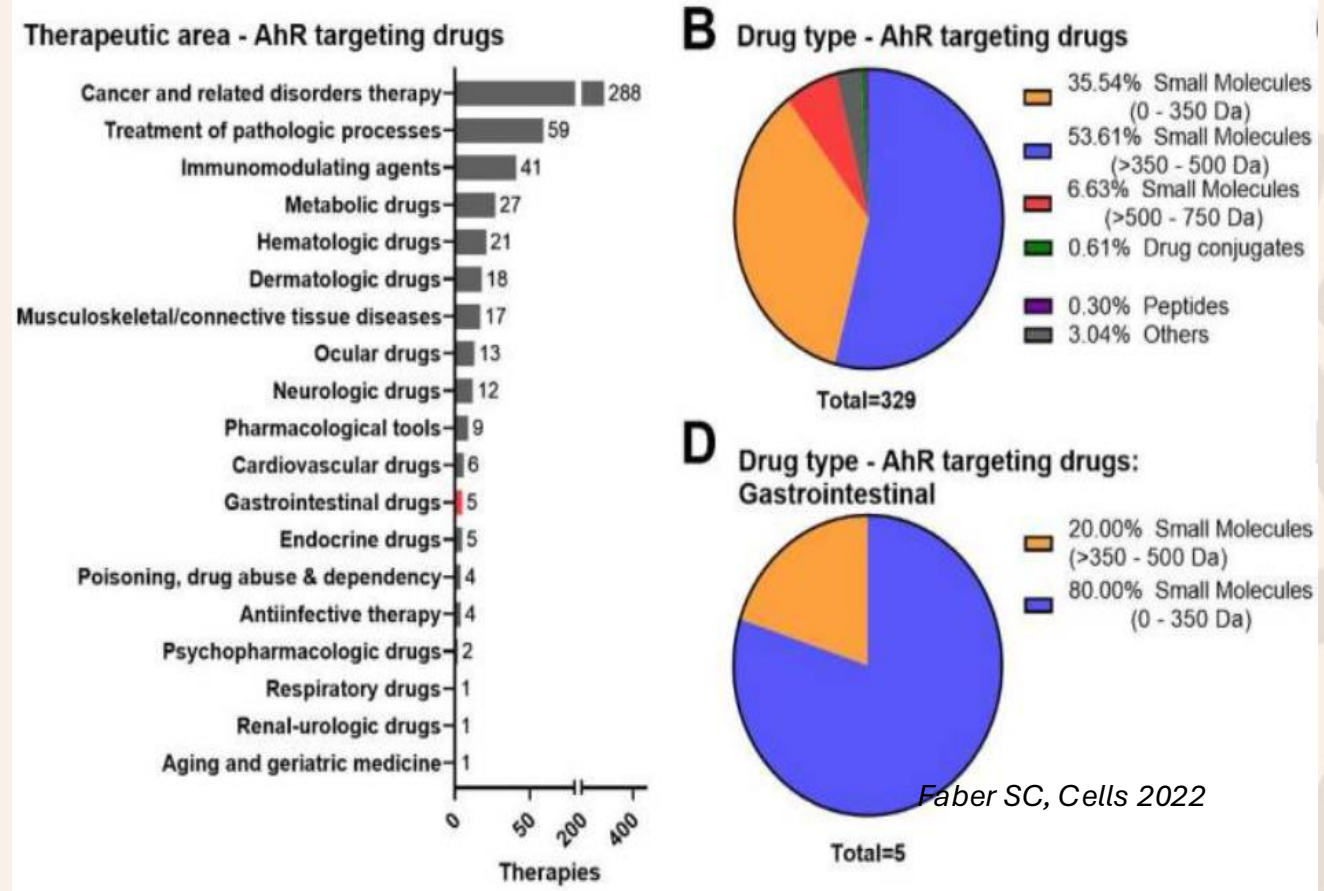
Tryptophan metabolites are ligands of AhR and induce its homeostatic activity in the gut



Tryptophan (Trp) metabolites and AHR are important for intestinal homeostasis



>240 AhR targeting agents are in development



Contraindications and Safety

Contraindications

- Patients with a personal or family history of PAH, DVT, or severe cardiovascular, or cerebrovascular disease.
- Patients who are pregnant or breastfeeding
- Patients with a chronic liver disease (PSC & Autoimmune Hepatitis)
- Patients with hypercoagulability

Safety Guide

- 2-3% experienced mild headaches during the first 72 hours. This is usually transient or responds to temporary dose-halving or 1-2 days halting treatment.
- 4-5% experienced mild transient elevation of liver enzymes. Blood tests are therefore recommended at week 6.
- Right-sided ischemic colitis or colonic intussusception were reported in very rare cases. If a patient reports new unusual abdominal pain, withholding CurQD is advised.
- Pulmonary atrial hypertension has been reported in very rare cases after prolonged use. Echocardiography is recommended for patients taking CurQD for over 6 months or experiencing symptoms of chest pain or shortness of breath.

CurQD Initiation: *Week 0*

Initiation of
Treatment

Follow-up: *Week 2*

Remote Clinical
Check-up for AEs

Follow-up: *Week 4*

Liver Function
Test

Re-evaluation: *Week 8*

Reevaluation of
Treatment

Using Nutraceuticals for IBD: Time for a change

EDITORIAL

Is it Time for the Alternative
to Move to the Mainstream?



Ashwin N Ananthakrishnan ¹

Affiliations + expand

PMID: 37453593

DOI: 10.1016/j.cgh.2023.07.003

Comment on

Curcumin-QingDai Combination for Patients With Active Ulcerative
Colitis: A Randomized, Double-Blinded, Placebo-Controlled Trial.

Ben-Horin S, et al. Clin Gastroenterol Hepatol. 2024. PMID: 37302449 Clinical Trial.

“The therapeutic landscape IBD has dramatically shifted over the past 2 decades with the approval of treatments... [that] have helped us achieve significantly higher rates of remission... However, despite this demonstrable success, many patients and health care providers continue to have concern about the long-term safety of these treatments... This generates a discussion of alternative approaches to manage IBD in a substantial portion of patient encounters. However, challenging the ability to have an informed discussion on the topic is the paucity of high-quality data to support efficacy of such approaches. **As treating providers, it is important for us to remain current in this rapidly evolving field of complementary and alternative medicine to guide our patients toward treatments that have the most robust established efficacy.**”

Take home messages

Follow the Evidence, not the Trend.

Nutraceuticals approaches (CurQD used as an example) can benefit clinical outcomes and address patients' personal wishes, but need to be:

- Evidenced based: Placebo-controlled trials
- Not OTC but guided management: By physicians/APPs/Dieticians
- Combinable : Integrated into standard care as adjunct treatment
- Positioning: An escalation-sparing treatment...
- We're far from interchangeable 'Botani-similars'....

THANK YOU

Sheba Research team



Missing but working hard:
Michal Amitai, Eyal Klang, Gilat Efroni

Research support

