Polyphenols

Discover the plant power of polyphenols and their interaction with health and disease.

+ ANTHOCYANINS
+ CURCUMIN
+ ELLAGIC ACID
+ EPIGALLOCATECHIN GALLATE (ECGC)
+ FLAVONOIDS
+ ISOFLAVONES
+ RESVERATROL

MetaXplore™
Powered by MiCROBA

What are polyphenols?

Polyphenols are plant phytochemicals (bioactive compounds produced by plants) and are grouped based on their structural characteristics.[1] More than 8,000 different types of polyphenol compounds have been identified; however, they can be broken down into four main structural groups:

- Flavonoids
- Phenolic acids
- Lignans
- Stilbenes

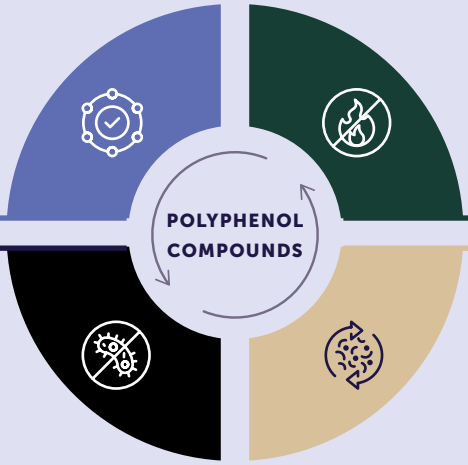
There are currently no daily targets for polyphenol intake, however a diet rich in polyphenols, such as the Mediterranean diet, is considered beneficial for supporting a resilient gut microbiome and for maintaining general health.

Polyphenols are predominantly found in fruits, vegetables, tea, coffee, chocolate, whole grains, nuts, seeds, and spices.

Polyphenol mechanisms

Antioxidant
The antioxidant action of polyphenols has been studied in humans via measuring total antioxidant capacity, superoxide dismutase and Malondialdehyde.[4-11]

Anti-inflammatory
It is hypothesised that polyphenols suppress inflammation by blocking the Nf-kB inflammatory pathway.[12-19]



Antimicrobial
From in vitro studies we see most polyphenols are able to inhibit the growth of a wide range of pathogens and pathobionts.[20-40]

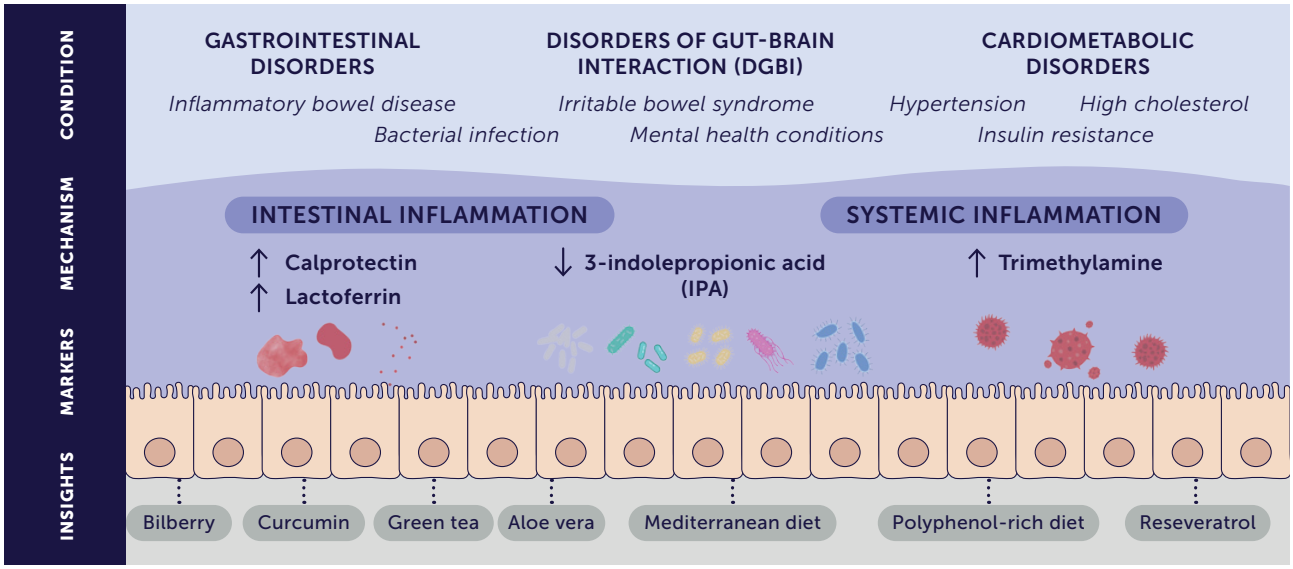
Prebiotic
An estimated 90-95% of dietary polyphenols reach the lower gut. Therefore, a significant proportion of polyphenols interact with gut microbiota.[2-3]

Are polyphenols prebiotics?

In 2017, the International Scientific Association for Probiotics and Prebiotics (ISAPP) decided that polyphenols should be considered prebiotics.[2] With 90-95% of polyphenols reaching the lower gut, their limited bioavailability may correlate with greater prebiotic effects.[3]

Polyphenols for gastrointestinal health and gut microbiome modulation

Polyphenol compounds interact with the gut microbiome and gastrointestinal environment in a variety of different ways, including exerting an influence on select gastrointestinal health markers, as well as some microbial markers. Some common presentations for polyphenol evaluation may include intestinal and systemic inflammation.



		MetaXplore	MetaXplore GI	MetaXplore GI Plus
Intestinal Inflammation	Calprotectin	✗	✓	✓
	Lactoferrin	✗	✓	✓
	3-indolepropionic acid (IPA)	✓	✓	✓
Sytemic Inflammation	Trimethylamine (TMA)	✓	✓	✓

Testing for invaluable insights

Testing the gut microbiome can provide insights into the potential for your patient's gut microbiome to impact their health. Equipped with this information, you can make informed clinical decisions and provide your patient with personalised polyphenol recommendations to better support their health.

Dietary interventions to enhance polyphenol intake

• dominant polyphenol in food item

	FLAVONOIDS								NON-FLAVONOIDS				
	Isoflavones	Anthocyanin	Flavanols		Flavonols		Flavanones	Flavones	Phenolic acids		Resveratrol	Lignans	Other
			EGCG	Other	Quercetin	Other			Ellagic	Other			
Fruits													
Apple, 1 cup				•									
Apricot, 1 cup												•	
Black elderberry, 1 cup		•											
Blackberry, 1 cup		•											
Blackcurrant, 1 cup		•											
Blueberry, 1 cup		•								•			
Grape, black, 1 cup		•		•									
Grape, green, 1 cup				•									
Kakadu plum, freeze dried, 1 tsp									•				
Nectarine, 1 cup				•									
Grapefruit, 1 cup							•						
Orange, 1 cup							•						
Peach, 1 cup										•			
Pear, 1 cup										•		•	
Plum, 1 cup		•		•						•			
Pomegranate, arils, 1/3 cup									•				
Prune, 1/2 cup										•			
Quince, 1/2 cup										•			
Red raspberry, 1 cup		•							•	•			
Redcurrant, 1 cup		•											
Strawberry, 1 cup		•		•									
Sweet cherry, 1 cup		•								•			
Vegetables and legumes													
Globe artichoke head, 1/2 cup								•		•			
Asparagus, 1/2 cup					•								
Broccoli, 1/2 cup						•						•	
Capers, 1/4 cup					•								
Celery, leaves, 1/2 cup								•					
Chicory, green, 1/2 cup										•			
Chicory, red, 1/2 cup										•			
Kale, 1/2 cup						•							
Olive oil, extra virgin, 1 tbsp													•
Olive, black, 1/2 cup										•			•
Olive, green, 1/2 cup										•			•
Onion, red, 1/4 cup					•								
Onion, yellow, 1/4 cup					•								
Parsley, 1/4 cup								•					
Shallot, 1 bulb					•								
Soy products, 1/2 cup	•												
Spinach, 1/2 cup						•							
Nuts & seeds													
Almonds and Hazelnuts				•									
Chestnut, 30g									•				
Flaxseed meal, 30g										•		•	
Pecan, 30g				•					•				
Walnut, 30g									•				
Grains (flours)													
Oat, whole grain, 1/2 cup										•			
Rye, whole grain, 1/2 cup										•			
Wheat, whole grain, 1/2 cup								•		•			
Cocoa													
Cocoa powder, 30g				•						•			
Dark chocolate, 30g				•						•			
Non-alcoholic beverages													
Black tea, 1 cup				•									
Coffee, filter, 1 cup										•			
Green tea, 1 cup			•	•									
Alcoholic beverages													
Red wine, 150mL		•		•									
Seasonings (dried)													
Cloves										•			
Rosemary										•			
Sage, common										•			
Thyme, common										•			
Turmeric													

Supplement dosage table

Specific polyphenols can be used to manage intestinal and systemic inflammation, as highlighted through MetaXplore's gastrointestinal and gut microbiome markers; calprotectin*, lactoferrin*, 3-indolepropionic acid (IPA) and trimethylamine.

Polyphenol	Health effect	Dosage	Duration	Reference
Aloe vera No established safe dose. Avoid if hydroxyanthracene derivatives are present (whole leaf extract or aloe latex) as evidence of genotoxicity.[43]	May reduce intestinal inflammation (MetaXplore GI and MetaXplore GI Plus measures intestinal inflammation via gastrointestinal health markers calprotectin and lactoferrin)	2 x 100mL/day (aloe gel)	4 weeks	[44]
	May reduce IBS symptoms	500mg/day (freeze-dried gel)	4 weeks	[45-46]
Bilberry Max dose: 160g considered tolerable limit Very high doses should be avoided in patients with haemorrhagic (bleeding) disorders.[47]	May reduce intestinal inflammation (MetaXplore GI and MetaXplore GI Plus measures intestinal inflammation via gastrointestinal health markers calprotectin and lactoferrin)	160g/day bilberry preparation equal to 95g dry weight (600g fresh fruit, equivalent to 840mg/day anthocyanins)	6 weeks	[47]
Curcumin No established safe dose (based on 2023 TGA report on potential hepatic effects).[48]	May reduce intestinal inflammation (MetaXplore GI and MetaXplore GI Plus measures intestinal inflammation via gastrointestinal health markers calprotectin and lactoferrin)	2 x 50mg/day (bio-enhanced); 2 x 1.5g/day; 1g/day	6 weeks; 1 month; 6 months	[49-51]
	Reduces CRP	≤700mg/day; Not dose-dependent (most studies ~500mg)	>7 weeks; Greatest effect seen at ~13 weeks	[12-13]
	Reduces IL-6	Not dose-dependent	Not duration-dependent	[12-13]
	Reduces self-reported gastrointestinal complaints	500mg/day	4 weeks	[52]
Epigallocatechin gallate (EGCG) Max dose: 300mg/day (risk of hepatic and gastrointestinal adverse effects if exceeded).[53-54]	May reduce intestinal inflammation (MetaXplore GI and MetaXplore GI Plus measures intestinal inflammation via gastrointestinal health markers calprotectin and lactoferrin)	May require >300mg/day. Need more studies to confirm if necessary.	28 weeks; 56 weeks	[55-56]
	May reduce fasting blood glucose	May require >300mg/day	>12 weeks	[57-59]
	May reduce TC and LDL-C	~200mg/day EGCG	3 months	[60-62]

Polyphenol	Health effect	Dosage	Duration	Reference
Ellagic acid Max dose: 2 x 500mg/day (limited number of studies. 2 x 500mg/day has been used safely for 12 weeks with no adverse effects).[64]	May reduce LDL-C	≥180mg/day	Not duration-dependent	63
	May reduce total triglycerides	≥180mg/day	≥8 weeks	63
	May reduce fasting blood glucose	≥180mg/day	≥8 weeks	63
	May reduce insulin	Not dose-dependent	≥8 weeks	63
	May reduce HOMA-IR	Not dose-dependent	Not duration-dependent	63
	May reduce CRP	180mg/day; 200mg/day; 2 x 450mg/day	60 days; 8 weeks; 8 weeks	14-16
	May reduce TNF-a	180mg/day; 200mg/day	60 days; 8 weeks	14-15
Isoflavones Max dose: No adverse effects at 300mg/day for 2 years or 120mg/day for 3 years.[70-71]	Isoflavone supplementation may improve symptoms of menopause (frequency of hot flashes)	30 to 80mg/day Supplements providing >18.8mg genistein for at least 12 weeks were more than twice as effective	6 weeks to 12 months	65-66
	Isoflavone supplementation may improve symptoms of menopause (severity of hot flashes)	30 to 135mg/day	12 weeks to 12 months	65-66
	Dietary soy intake may improve symptoms of menopause	115.9g/day soy intake; 86g cooked soybeans	N/A; 12 weeks	67-69
Resveratrol Max dose: 150 - 450mg/day (recommended by EFSA, though no treatment-related effects observed for <1g/day in studies up to 3 months).[76-77]	May reduces plasma trimethylamine (TMA)/ trimethylamine N-oxide (TMAO) (MetaXplore, MetaXplore GI and MetaXplore GI Plus measures systemic inflammation via microbial marker trimethylamine (TMA))	2 x 300mg	28 days to 8 weeks	72-73
	May reduce CRP and TNF-a	Not dose-dependent	Not duration-dependent	17
	May reduce blood pressure	300mg/day; 600-1000 mg/day	At least 3 months; 2-3 months	74
	May reduce LDL-C	≥500mg/day	≥12 weeks	75
	May reduce total cholesterol	Not dose-dependent	Not duration-dependent	75

CRP: C-reactive protein
IL-6: Interleukin-6
TC: Total cholesterol
LDL-C: Low-density lipoprotein-cholesterol
HOMA-IR: Insulin resistance
TNF-a: Tumour necrosis factor alpha
TMA: Trimethylamine
TMAO: Trimethylamine N-oxide

Nutrient and drug interactions

Diet and nutrients

Iron	Polyphenols have iron-chelating effects by forming complexes with iron, inhibiting absorption. Polyphenol supplementation may have an inhibitory effect on serum iron concentration and transferrin saturation.[78] 300 mg of EGCG has been shown to significantly reduce iron absorption.[79]
Folic acid	300 mg of green tea extract has been shown to potentially reduce absorption of folic acid supplementation.[80]
High fat foods	Compared to a standard breakfast, a high-fat breakfast delays the absorption and reduces the exposure to resveratrol.[81] On the other hand, dietary fat has been shown to increase quercetin bioavailability.[82]

Drugs

Polyphenol	Drug	Exposure	Proposed mechanism	Reference
Curcumin	Sulfasalazine	Increased	Inhibited BCRP	83
	Talinolol	Decreased	Induced P-gp	84
	Caffeine, theophylline, clozapine, and acetaminophen (not yet assessed)	Increased	Inhibited CYP1A2	85
	Caffeine, nicotoine and cotinine (not yet assessed)	Decreased	Induced CYP2A6	85
Resveratrol	Warfarin	Increased	Inhibited BCRP* and CYP2C9	86
	Losartan	Increased	Inhibited CYP2C9	87
	Buspirone	Increased	Inhibited CYP3A4	87
	Dextromethorphan	Increased	Inhibited CYP2D6	87
	Caffeine	Decreased	Induced CYP1A2	87
Isoflavones	Theophylline	Increased	Inhibited CYP1A2	88
	Midazolam	Decreased	Induced CYP3A4	88
	Celecoxib*	Increased	Inhibited CYP2C9	88
	Paclitaxel*	Increased	Inhibited CYP3A4 and P-gp	88
	Repaglinide* and omeprazole*	Increased	Inhibited P-gp	88
	Imatinib* and carbamazepine*	Decreased	Induced CYP3A4	88
Ellagic acid	Metoprolol*	Increased	Inhibited CYP2D6	89
	Diltiazem*	Increased	Inhibited CYP3 and P-gp	90

Polyphenol	Drug	Exposure	Proposed mechanism	Reference
Green tea	Simvastatin and tacrolimus	Increased	Inhibited CYP3A4 and P-gp	91
	Sildenafil	Increased	Inhibited CYP3A4	91
	Buspirone	Increased	Inhibited CYP3A4	92
	Rosuvastatin and nadolol	Decreased	Inhibited OATP1A2 or OATP2B1	91
	Digoxin	Decreased	Induced P-gp	93
Quercetin	Cyclosporine	Increased	Inhibited CYP3A4	94
	Pravastatin	Increased	Inhibited OATP1B1	95
	Fexofenadine	Increased	Inhibited P-gp	96
	Talinolol	Decreased	Induced P-gp	97
	Midazolam	Decreased	Induced CYP3A	98
	Paracetamol*	Increased	Inhibited P-gp	99

NB: this is not an exhaustive list of potential drug-polyphenol interactions.
*Preclinical evidence in animals: clinical experiments are needed to assess these drugs when concomitantly administered with this polyphenol

Polyphenol safety considerations

Polyphenol	Max dose	Adverse events	References
Resveratrol	150 - 450mg/day	Generally well-tolerated but GI symptoms, especially diarrhoea, are common (mild up to 1.5g/day, most common when of at least 2.5g/day). EFSA Panel suggests 150mg/day. resVida® is a trans-resveratrol supplement with GRAS status at 450mg/day. Caution when taking with warfarin as may increase anticoagulant effects.	76-77
Ellagic acid	2 x 500mg/day	Limited number of studies. 2 x 500mg/day has been used safely for 12 weeks with no adverse effects.	64
Curcumin	No established safe dose	2023 TGA report on potential hepatic effects determined there is no established safe dose. There are new TGA label requirements for curcumin products. Liver injury is idiosyncratic; therefore, dose cannot predict it.	48
Aloe vera	No established safe dose	Avoid if hydroxyanthracene derivatives are present (whole leaf extract or aloe latex) as evidence of genotoxicity.	43
EGCG	300mg/day	Mild-moderate GI symptoms observed in 400 to 4000mg/day. Liver injury can occur when consumed in supplement form but does not appear to occur from green tea beverage consumption. Highest incidence from Polyphenon E supplement.	53-54
Isoflavones	No adverse effects at 300mg/day for 2 years or 120mg/day for 3 years	In 2015, the European Food Safety Authority declared soy isoflavones do not adversely affect the breast, thyroid, or uterus of postmenopausal women and is in support of their safety. However, more research is required on utero isoflavone exposure and the effects of isoflavone on thyroid in cases of iodine deficiency.	70-71

EFSA: European Food Safety Authority

Framework for personalised polyphenol prescription in clinical practice

Clinical presentations	Intestinal inflammation (inflammatory bowel disease, irritable bowel syndrome, pathogenic infection, ischaemic colitis, food allergy)	☐
	Systemic inflammation (autoimmune disease, cardiovascular disease, metabolic disease, mental health conditions)	☐
Initial consultation	**Patient assessment and gastrointestinal and gut microbiome testing**	
	Evaluate patients' dietary habits, MEDAS score, health conditions and medication use	☐
	Referral for MetaXplore, MetaXplore GI or MetaXplore GI Plus report	☐
	Mediterranean diet with polyphenol rich foods	
	Encourage patients to follow a Mediterranean style diet that includes a variety of polyphenol-rich foods	☐
	Provide practical dietary advice and recipes to help patients integrate these foods into their daily meals	☐
Follow-up consultation	**Review of gut microbiome and gastrointestinal results**	
	Review MetaXplore, MetaXplore GI or MetaXplore GI Plus report for: • Calprotectin • Lactoferrin • 3-indolepropionic acid (IPA) • Trimethylamine (TMA)	☐
	Polyphenol dietary and supplement prescription, if required	
	Manage out of range markers with SPECIFIC polyphenol dietary or supplement interventions if required	☐
	Consider nutrient and drug interactions, and polyphenol safety before polyphenol supplement prescription	☐
Subsequent follow-up consultations	**Monitor and adjust as needed**	
	Monitor the response and tolerability to the intervention	☐
	Assess patients' symptom/condition improvement	☐
	Amend the dose or change the intervention, if needed	☐
Re-test	Re-test between 3-6 months to understand effectiveness of polyphenol intervention	☐

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