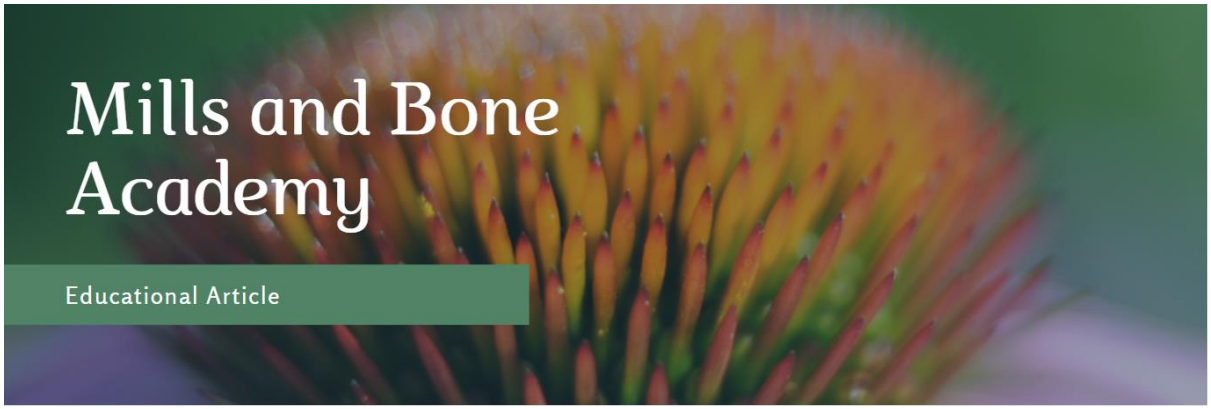


Turmeric and Curcumin: Powered by the Gut! –

Simon Mills

Summary

There is an increasing research case that reinforces an old assumption, that turmeric is primarily a digestive remedy. In modern times it has however been assumed that the most active constituent, the yellow polyphenol curcumin, is necessary to deliver the benefits in modulating inflammatory responses around the body. However assimilation of curcumin is poor and so it is reassuring that there are a number of mechanisms that do not rely on curcumin absorption for this benefit.

In the review we will look at digestive and microbiome levers on health which are likely to be activated by curcuminoids and other turmeric constituents, and will conclude that the gut is a good place for them to be.

'Igniting digestive fire': turmeric's traditional reputation

As well as being one of the most widely consumed spices in India (with average daily consumption of several grams even in remote rural populations) turmeric has been one of the most valued remedies in Ayurvedic medicine. Here it has been seen as a heating and drying remedy that moves the circulation, and which clears digestive-based toxins (ãma or 'damp') especially from the lower abdomen and pelvic areas. A key concept in Ayurveda is that of supporting agni (fire) in the digestion, as a metaphor for all digestive and metabolic processes at the core of health. Sanskrit descriptors of turmeric include deepana – enkindling the digestive fire, and pachana - helping digestion. In Ayurvedic medicine it is used as a stomachic, for poor digestion, vomiting in pregnancy and liver disorders, like other warming spices to manage fevers, as a convalescent tonic and as a detox remedy in skin conditions.

In traditional Chinese medicine turmeric rhizome is said to move blood and qi and have analgesic properties. It is used to treat chest and abdominal pain and distension, jaundice, frozen shoulder, amenorrhoea due to blood stasis and postpartum abdominal pain due to stasis. The focus on abdominal congestion is

very close to that of Ayurveda. One modern indication is viral hepatitis.

In traditional Western herbal medicine, turmeric was regarded as an aromatic digestive stimulant and as a treatment for jaundice.

All these traditional indications for turmeric reflect its spicy stimulation of the circulation and especially direct effects on digestive and hepatic functions. These can now be elaborated.

Turmeric phytochemistry: more than 'curcumin'

Although turmeric's most prominent active constituent is often referred to as if it was a single chemical entity, 'curcumin' is actually a variable mix of three non-volatile diarylheptanoids (curcuminoids): diferuloylmethane (curcumin I), desmethoxycurcumin (curcumin II), and bisdesmethoxycurcumin (curcumin III). Sample-to-sample variability of curcuminoids significantly reduces the consistency of research findings for the effects and bioavailability of 'curcumin'. Further clouding the issue is the metabolism of curcuminoids as they pass through the gut, by the microbiome and by intestinal cell wall enzymes. Microbiome metabolites include demethylcurcumin, bisdemethylcurcumin, dihydrocurcum, tetrahydrocurcumin and ferulic acid (discussed later). Gut wall metabolites include curcumin glucuronide, curcumin sulfate, tetrahydrocurcumin, and hexahydrocurcumin. There is mixed evidence for the individual activity of these metabolites but enough to suggest that they may contribute with other non-curcumin constituents to the spectrum of turmeric's effects.

Novel curcumin formulations have emerged which are established as providing increased bioavailability, with the prospects of direct curcuminoid activity in the tissues, even through the blood-brain barrier to benefit neurological disorders. However this review is on the impact of generally available powdered turmeric rhizome and its immediate derivatives.

There are many other compounds in turmeric as a whole. One report lists 22 diarylpentanoids and diarylheptanoids (like curcumin); 8 phenylpropenes and other phenolics, 68 monoterpenes, 109 sesquiterpenes, and assorted diterpenes, triterpenoids, sterols, alkaloids, and other compounds. An oil fraction makes up 0.7–0.8% of turmeric's constituents and is responsible for the spice's aromatic taste and smell: it is dominated by sesquiterpenes, most abundantly bisabolanes: aromatic ar-turmerone (28%), β-turmerone (17%), curlone (14%), 2-carene (5%), zingiberene (4.37%), sesquiphellandrene (6%), ar-curcumene (3%), and linoleic acid (5%). Some of these components demonstrate activity comparable to nonsteroidal anti-inflammatory drugs, and curcumin-free turmeric can be as effective as curcumin-containing turmeric.

This complexity is reflected in a wide spectrum of biovailability and likely broad range of

activity through the body. However all the research indicates that the 'curcumin' itself, however defined, is barely accessible to the body tissues from native turmeric. Indeed perhaps only 1% of curcumin consumed actually gets through the gut wall into the body from this source. Although as noted above, more bioavailable formulations have become available to help get around this challenge, to find benefits that do not rely on curcumin absorption will both provide plausible additional reasons to use the remedy and underpin its strong traditional reputation.

Why focusing on the gut can be productive

There are excellent reasons to deliver benefits within the confines of the gastrointestinal tract. Its lining presents thousands of square metres of complex surface to the outer world and to the inner microbiome. The main inputs into the decision-making processes involved in digestion are a vast array of receptors and sensory tissues along that surface. Each of these provides signals for not only for motor and secretory functions elsewhere in the gut, but elsewhere in the body.

Even modest gut surface stimulation can be levered into major effects. This leverage follows from the gut being:

- most of the immune system (as the main route of access for foreign and pathogenic materials)
- the home of the body's largest reservoir of genetic material, the microbiome
- the body's largest endocrine organ
- the major eliminatory organ
- a source of reflex responses onto other body functions eg liver, lungs, circulation and kidneys
- the key determinant of cellular energy supplies (blood sugar levels)
- the recycler of metabolites via bile, bowel, and microbiome
- the source of all physical and much emotional nourishment and replenishment (sharing common neurohormonal mechanisms with the CNS).

Effects of turmeric constituents in the gut

Curcumin and turmeric as a whole have many important direct effects on gut functions that do not rely on curcumin absorption.

1) Turmeric is a prebiotic (or 'postbiotic'?). Turmeric has been shown beneficially to alter the gut microbiome, with relatively more Lactobacillus and Bifidobacter populations, generating increased butyrate levels, and fewer pro-inflammatory Enterobacteria and Enterococci. In human subjects curry with turmeric significantly increased breath hydrogen compared with curry not containing turmeric, suggesting that dietary turmeric activates carbohydrate colonic fermentation.

However turmeric is not a conventional prebiotic. Its effects here appear to be driven largely by indirect effects based on alterations in host physiology such as changes in barrier function, or through selective survival of local bacteria or other microorganisms. A

bidirectional relationship between curcumin and the microbiome has been identified: as has been noted curcumin is transformed by the microbiota into more active metabolites; these in turn increase microbiomic diversity, reduce absorption of inflammatory bacterial lipopolysaccharides (LPS – see below) with quantifiable benefits for IBD, hepatic stenosis, tumorogenesis and neurological disease.

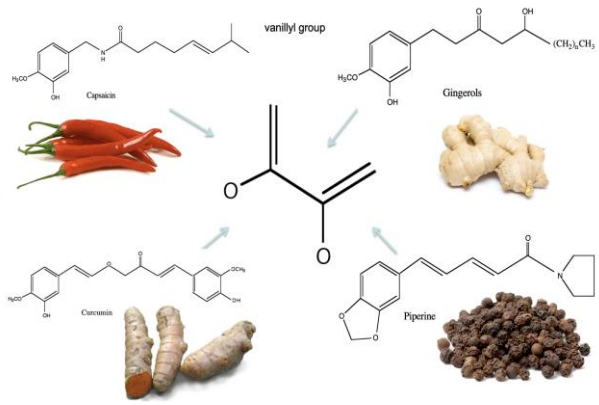
A term that can be used to describe the beneficial effects of herbs on the microbiome reflects such bidirectional activities. 'Postbiotic' refers to effects on the microbiome that generate from the consequences of microbial action on the initial material. It is appropriate to begin to apply this descriptor to curcumin, polyphenols and other secondary plant metabolites.

2) Curcumin reduces systemic inflammation via its effects on the gut wall. Curcumin inhibits Toll-like receptors (TLRs): TLR2, TLR4 and TLR9, so as to reduce their cascade of signalling events leading to proinflammatory cytokine production. TLR4 in particular responds to bacterial lipopolysaccharide and there is evidence that curcumin can modulate its pro-inflammatory activity. Perhaps most significantly for systemic inflammatory disease curcumin reduces gut leakiness to pro-inflammatory factors (such as cytokines and lipopolysaccharides) and also to bacterial or virus infection from the intestine. , Direct benefits on inflammatory conditions elsewhere in the body include chronic kidney disease. This mechanism has also shown promise in the management of inflammatory bowel disease, including Crohn's disease.

Curcumin reduces leaky gut patterns in a number of models, including the activity of gut wall proinflammatory factors such as cyclooxygenase-2, 5-lipoxygenase, inducible nitric oxide synthase (iNOS),TNF-□, IL -1, -2, -6, -8 and -12, TLR 4, and Nf-kappa-β. It mends intestinal cell wall junctions, blocks gut surface enzymes (eg alkaline phosphatase), transcription factors, and growth factors. It reverses the carcinogenic effect of bile acids in reflux oesophageal cancer, in part through suppression of cyclooxygenase-2 (COX-2) gene expression.

3) Turmeric is a choleretic. It stimulates gallbladder emptying - by between 25-50%. , It was found bisacurone B was the most potent choleretic ingredient, followed by ar-turmerone, bisdemethoxycurcumin, demethoxycurcumin, and then curcumin. The potential benefits of this activity are becoming clearer. Bile acids speed intestinal transit and secretions ('endogenous senna'), they increase absorption through facilitated mucosal permeability, stimulation of GPBAR1 receptors or through the detergent properties of bile acids, and mobilise the gut-brain axis by activating the secretion neurohormones like 5HT. Gut microbiota deconjugate these bile acids to secondary metabolites and are important regulators of the total bile acid pool as well as of their composition and impact on the gut. This is referred to as bile-microbiome crosstalk: turmeric effectively engages in this crosstalk by increasing microbiotic metabolism of bile acids and reducing consequent laxative action. ,

4) Turmeric is a spice. Like active principles of other spices cayenne, ginger and black pepper, curcumin has a vanillyl group (see figure) and can stimulate the transient receptor potential vanilloid receptor 1 (TRPV1) on the gut wall surface, leading to increased blood flow and muscle relaxation, and therapeutic benefits similar to those of ginger. In one study curcumin's observed benefits in test models of inflammatory bowel disease was abolished by the TRPV1 antagonist capsazepine. Follow-up in vitro observations suggest that the TRPV1 receptor is more sensitive to this effect in inflamed tissues.



5) Turmeric modulates intestinal activity. In the paper on human subjects above curry with turmeric also shortened small-bowel transit time suggesting that turmeric can increase bowel motility.11 Turmeric has calcium-channel blocking spasmolytic effects on the gut wall greater than either verapamil or curcumin alone. These findings added to the effect on bile above reinforce the view that turmeric can stabilise gut motility from either extreme.

6) Curcumin works on the gut to reach the brain. It reduces markers of anxiety, depression and IBS via 5HT-dependent gut wall receptors.

Impacting the microbiome is better with low bioavailability

One of the clear conclusions from prebiotic research is that for plant constituents to influence the microbiome they have to avoid assimilation so they can reach the lower reaches of the gut. This is obvious for fibre, complex carbohydrate, gum and other conventional prebiotic foods but it has also become clear from discovering the prebiotic properties of polyphenols, , . saponins, and acrid constituents like capsaicin. ,

Curcumin is a polyphenol and also shares properties of acrids and it has been demonstrated that its prebiotic effects are in direct proportion to its lack of availability.13

It is likely that as the ancients knew all along, much of the effect of turmeric is in the gut. This applies especially for curcumin: as Dr Shobha Ghosh Professor of Medicine and Physiology in the Virginia Commonwealth University School of Medicine put it: "curcumin does not need to be absorbed to bring about its effects since it has profound effects on the intestinal wall and can effectively reduce inflammation by this mechanism".18

Simon Mills

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