Cell-Logic®

Specialists in Nutrigenomics, Nutraceuticals & Functional Foods

PRODUCT ADVISORY STATEMENT (P.A.S.)

Guide to Effective Prescription of Sulforaphane in Digestive Dysfunction with Cautions and Contraindications

(Applicable to EnduraCell®, EnduraCell® PLUS, DefenCELL®, PomGenex and CardiOS, together with Sulforaphane yielding Integra Nutritionals products)

OVERVIEW: Very occasionally, adverse effects have been reported after ingestion of either fresh broccoli sprouts or supplements manufactured from fresh sprouts. These effects are typically gastro-intestinal in nature and may include nausea, bloating, gastro-abdominal discomfort, and diarrhoea. The limited data available seem to indicate that such effects are generally limited to those with pre-existing gastro-intestinal conditions and in particular to those with *dysbiosis* associated with a perturbed gut ecosystem. Pathogenic microbes may or may not be present; there may simply be an imbalance in the resident microbes.

Where a clinician may conclude that the patient is intolerant to the sulforaphane-yielding food or supplement, a closer look at the relevant mechanisms of action reveals that not only can the symptoms be readily managed – but that continued appropriate prescription is likely to significantly improve the patient's gut function. A rationale and guidelines for managing such cases follows.

What is Sulforaphane – and does it affect a person genuinely allergic to sulfur?

Sulforaphane (SFN) is the most well-researched of the bioactive molecules derived from cruciferous vegetables, with its potent preventive and therapeutic effects acknowledged.[1, 2] However, having *'sulf'* as part of its name often sees it mistakenly confused with *'sulfa'* drugs, a class of antibiotic to which reactivity or allergy is common. Being reactive to a *sulfa* drug is entirely different from being reactive to *sulfur*, a critically essentially food molecule. Even so, an individual may be both allergic to *sulfa* drugs and intolerant to *sulfur.* Other food intolerances may co-exist.

Understanding common causes of abnormal digestive function

There are several sulforaphane-related mechanisms that can be responsible for temporary discomfort and associated changes in digestive function. In most cases, reactivity is due to an imbalance in the population of microbes inhabiting the gut lumen. Where such an imbalance exists, it is likely there is significant inflammation in the cells lining the digestive tract. When this occurs, normal digestive functions such as mucous secretion, secretory IgA secretion, enzyme synthesis and motility can all be compromised.

How does diet-derived Sulforaphane influence gastro-intestinal function?

There are several inbuilt mechanisms that are activated by sulforaphane in the digestive tract and its underlying immune cells. The six main mechanisms are shown in the diagram on the next page. Because sulforaphane can activate natural *anti-microbial synthesis* in the gut epithelial cells, die-off of the *'undesirable'* microbes may occur.[3] As these microbes (typically bacteria) die, they release waste materials which must then be detoxified by the host. An impaired gut barrier allows ready absorption of these waste molecules into the circulation. An adverse reaction to SFN typically identifies dysbiosis which it can subsequently correct.

What if there are pre-existing digestive symptoms?

Where an individual has pre-existing digestive symptoms, the introduction of sulforaphane can sometimes appear to exacerbate the condition as it works to normalise essential functions. The following instructions are designed to limit the symptoms whilst, at the same time, allowing normal function of the gut epithelium to be restored.

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Clinical relevance

Managing the effects of gut dysbiosis and restoring homeostasis are fundamental priorities that must be addressed if systemic health is to be achieved. Ongoing dysbiosis and reduced gut barrier function are seen to be at the core of chronic and acute disease. The *Gut Ecology & Metabolic Modulation Protocol* **(G.E.M.M.)** is founded on these principles, restoring not just digestive abnormalities but also metabolic and other systemic conditions.

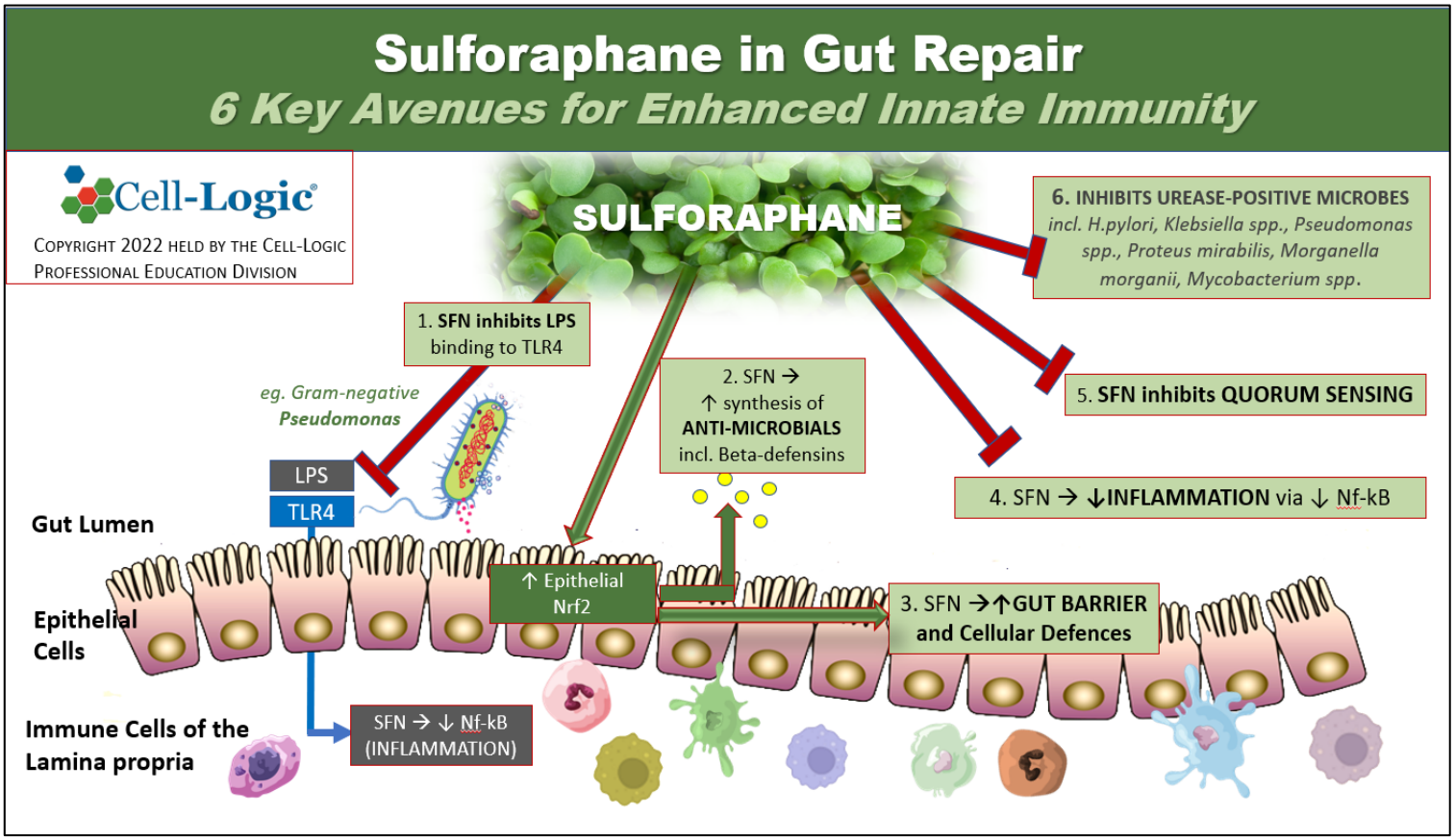
Dose Titration

In sensitive individuals, titration up to full dose from a low starting dose allows progressive correction of the underlying causes without overloading the patient's ability to adapt. The goal is to enable the patient to tolerate the full sulforaphane dose at a pace that eliminates symptoms whilst simultaneously restoring homeostasis.

Instructions for addressing SFN reactivity in sensitive patients

1. Discontinue all source of SFN – cruciferous vegetables, broccoli sprout powder and/or capsules.
2. Assuming symptoms abate, resume SFN at a very small dose. This dose may be as little as will fit on the tip of a sharp vegetable knife blade. EnduraCell® powder is the best option, although capsules can be opened.
3. Take one such dose daily for a few days to ensure that the gastrointestinal system feels comfortable.
4. Gradually increase the dose by taking a second similar dose each day.
5. Repeat the process by increasing a little each day, monitoring symptoms to determine daily dose.
6. Typically, within 2 weeks, the standard recommended dose will not produce significant ill effects. In severe cases, tolerance may take weeks more to achieve. Be guided by the patient's response.
7. Those with known dysbiosis or other gastrointestinal issues will typically find that these symptoms have either partially or fully cleared. Cruciferous vegetables can be re-introduced at this stage.
8. Where a patient has been intolerant to other foods, their introduction can be trialled one at a time.

SAFETY: Consumers may notice standard and enhanced dose ranges on the labels of PomGenex, EnduraCell® 80g Powder, EnduraCell® BioActive 80 capsules and EnduraCell® PLUS 60 capsules. SFN has been found to be safe at higher doses, and the enhanced dose may be required to exert significant effects.[4]



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MECHANISMS ASSOCIATED WITH SULFORAPHANE'S ACTIONS IN THE GUT

EnduraCell® is a 100% whole dried broccoli sprout material that is available as a powder or as an ingredient in several of our formulations. The EnduraCell® ingredient has no additives of any kind; nothing but water has been removed to produce this exceptionally high sulforaphane-yielding material. EnduraCell® is manufactured to retain the glucoraphanin precursor and the myrosinase enzyme so that sulforaphane is enzymatically synthesised when the powder becomes moist – either by stirring into water – or when the vegetable capsule dissolves.

EnduraCell's Gut Defensive Mechanisms

The points below relate to the numbering system on the accompanying diagram.

1. SFN inhibits LPS binding to inhibit Inflammation: Gram-negative bacteria carry lipopolysaccharides (LPS) on their outer surfaces. (LPS is also described as *Endotoxin*). When LPS attaches to the epithelial receptor TLR4, it activates signalling mechanisms that lead to inflammation. SFN inhibits the binding of LPS to TLR4, thereby reducing the undesirable pro-inflammatory stimuli typical of gram-negative bacteria. This is one of several ways in which SFN downregulates uncontrolled inflammation.

2. Anti-microbial Effects: SFN upregulates the synthesis and release of endogenous anti-microbials that include *beta-defensin* which selectively targets undesirable microbes without adversely affecting the commensals. *Beta-defensin* and other endogenous anti-microbials protect the host against pathogens.[5] In a dysbiotic individual, this can result in bacterial *die-off*, often accompanied by release of the LPS. Release of LPS contributes to unpleasant gastro-intestinal symptoms as well as to metabolic disturbance.

3. Gut Barrier: A dysfunctional gut barrier results from both exogenous and endogenous factors; the latter include imbalances in *inflammation-redox status*, *elevated HbA1c* and more; SFN beneficially influences upstream mechanisms to restore the gut barrier. Where bacterial die-off occurs in a dysbiotic individual with impaired barrier function, potentially-toxic molecules travel via the portal circulation to the liver where they must be detoxified. If the process is too rapid, unpleasant systemic symptoms may result.

4. Cellular defence activation – anti-inflammatory: The most-studied mechanism associated with SFN is its role in upregulating the defensive processes intrinsic to human cells; this it does by activating the transcription factor, Nrf2. Activating the Nrf2 pathway reduces oxidative stress and uncontrolled inflammation whilst simultaneously down-regulating the pro-inflammatory transcription factor, NF-kB. In so doing, SFN helps to restore gut-immune homeostasis.

5. Quorum sensing - Biofilm degradation*: In vitro* studies have shown that SFN can degrade periodontal biofilms that can prevent the resolution of infections, thereby exposing the microbes to attack by elements of both the innate and adaptive immune system.[6] Mucosal biofilm communities are also known to inhabit the human intestinal tract,[7] with the potential for SFN to disrupt these biofilms. In so doing, a significant population of microbes is released into the intestinal mucosa, upregulating and potentially overloading detoxification pathways.[8-10] This is why guided introduction of SFN is important in dysbiotic individuals.

6. Urease inhibition: SFN is a urease inhibitor and has been shown to block the ability of *H.pylori* to produce *urease*, the enzyme responsible for the development of gastric inflammation and potential gastric tumour development. Many other pathogens/pathobionts are *urease-positive* and include *Klebsiella, Staphlococcus aureas, E. coli, Morganella, Pseudomonas* and many others. *Mycobacteria* (mould) are also urease positive. It is not known if urease-positive organisms other than *H. pylori* are responsive to SFN.[9-11]

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CAUTIONS AND CONTRAINDICATIONS

1. Direct-acting antioxidants

When mega-doses of direct-acting antioxidants are consumed, the cell may become saturated, masking the pro-oxidant signals the cell needs to defend itself via Nrf2. Unless there is deficiency, vitamin C and any other direct-acting antioxidant supplements like A, E, beta-carotene & NAC, will inhibit the cell's ability to upregulate its own antioxidant, detoxification and other cytoprotective genes. If needed at all, antioxidant supplements should be reduced to quantities no greater than RDI levels found in a plant-rich diet. The flaws of antioxidant supplementation in this context are evident in clinical trials.[12]

2. Cancer and treatments: Chemotherapy and Radiation

Because cancer cells *'hijack'* the cell's defence mechanisms, it is unknown whether SFN, GliSODin or other protective plant molecules in normal cells might also increase a cancer cell's ability to protect itself. It is therefore advisable to avoid prescribing SFN, GliSODin and other concentrated plant extracts in those diagnosed with cancer - or undergoing treatments such as chemotherapy and radiation.

3. Anti-coagulant medications

The RDI for Vitamin K1 is 700 mcg. A mature broccoli vegetable contains 85 mcg of Vit K1. The Vitamin K1 content of broccoli sprouts is low in comparison, with one 700 mg capsule of EnduraCell® BioActive containing approximately 7 mcg of Vitamin K1. *While Vitamin K2 appears not to interfere with coagulation, it is recommended that the patient's clinician be consulted to prescription of CardiOS.*

4. Goitrogens and thyroid function

Broccoli sprouts do not contain any significant goitrogens as found in the mature broccoli vegetable, so there are no contraindications to prescribing Cell-Logic's broccoli sprout formulae in thyroid conditions.

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