Review Article

Is this a Perfect Functional Meal for Mucosal Tolerance?

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Is this a Perfect Functional Meal for Mucosal Tolerance?

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Functional and pathological digestive tract conditions reflect a change in the relationship between the host microbiota and the mucosal immune and nervous system. These result in a wide range of distressing symptoms for which there are a variety of strategies, but no single intervention of consistent benefit. A component of patient care we sometimes overlook is that of the application of therapeutically relevant foods. For over 20 years I have been using a tried and tested formula that contemporary scientific research is now explaining why it has proven so effective for many patients.

What do I mean by effective? – Changes in inflammatory markers, reduced need for anti-inflammatory medication, better gastrointestinal function, weight loss, mood uplift and change in colonic and small intestinal flora ratios with improved digestive and eliminative function fit the bill for me.

In part these changes in symptoms are due to changes in dendritic cell (DC) regulatory function and increased oral tolerance which I hypothesise is due to increased regulatory T cell (Treg) promotion in the periphery especially in the GI Tract. This immune modulating food combination may be eaten for breakfast and dinner or as a meal substitute (no more than 1 substitution per day for many days) and as a quick and soothing snack.

Reactivity to Apples

I accept that there are patients that display reactivity to apples – the principle ingredient of this meal- and in part this is due to cross reactivity with birch pollen or latex allergy, and for others it relates to lipid transfer protein reactivity. For them, exchanging the apples for pears with all the other ingredients may offer a satisfactory alternative but as always must be judged on outcome or relevant investigations which may include changes of apple selection.[1]

Stewed Healing Apples and Immune Cofactors

Recipe:

Ingredients for primary stage

- 6 Bramley cooking apples (or apples of choice preferably grown organically)
- 1/2 cup water
- 1/2 cup raisins/sultanas
- 2 tsp. cinnamon

Directions

Peel and core the apples and chop them into small pieces.

Put all the ingredients in a covered, heavy-bottomed pan and cook for about 15 minutes, stirring regularly. Cook until soft with rough shapes, no longer identifiable as apple slices. The colour should be a russet brown with the cinnamon effect.

These may be eaten warm, or cold. I suggest making up as many ramekins (sized to hold 1 - 1.5 apple equivalent in each and covered and put in the fridge for easy recovery and to avoid food deviation due to lack of availability and so maintain compliance.

Ingredients for secondary stage

- 1 tsp. of larch arabinogalactans stirred into the apple to add sweetness - if required
- 1 Saccharomyces Boulardii 250mg capsule sprinkled on the top – or swallowed separately
- 1 mix of Bifidobacteria (mixed strains) (500mg) 5billion CFU sprinkled on top – or swallowed separately
- 1 x LGG sprinkled on top – or swallowed separately
- ½ container of organic natural yogurt (dairy) or soy equivalent approx. 75mg
- Add 6-8 blueberries and 4-5 almonds in their skins
- Finally, if required, a teaspoon of Manuka honey

The Scientific Rationale.

Foods confer information to humans through the direct delivery of micro and macronutrients via different signalling mechanisms. The immune system in the gastrointestinal system is a highly active and vital component of human health and its commensal bacterial load, in conjunction with the foods selected confer a wide range of opportunities for the delivery of specialised data to alter genetic and non-genetic derived immune outcomes.

> ***The principle food group in this dish is apple, the reason being that they are generally well tolerated, enjoyed and well-studied. They are also easy to cook and for patients with limited access to cooking facilities or a lack of interest in cooking this dish makes a simple but powerful connection between food and health.***

Allergy Protection

In analyses of individual foods, intake of apples/pears and carrots (all favourites of mine) was inversely associated with rhinitis, asthma, and atopic sensitisation. Essentially the more

you ate of these foods the better equipped your immune system is to handle antigen exposure.[2]

Antibiotic Impact

The However, the positive health effects of apple-derived polyphenols which from in vivo studies have been identified as some of the key immune modulating elements that give apples their therapeutic value still depend on their absorption, metabolism, distribution, and elimination from the body after consumption. This process requires the availability of relevant commensal organisms and the absence of antibiotics. Antibiotics produce adverse alterations of polyphenolic breakdown.[3]

Phenolic Compounds

Apples vary in their phenolic content, Honeycrisp and Red Delicious (USA) varieties had the highest total phenolic contents in one study and a there was significant correlation with antioxidant capacity ($r = 0.91$).[4]

At individual compound level, epicatechin and procyanidin B2 were the major contributors to the antioxidant activity of apple.[5]

> ***The phenolic compounds in apples are also indicated for use in common chronic conditions; the consumption of apples could provide health benefits by reducing the risk for chronic diseases such as metabolic syndrome disease, including type 2 diabetes.***[6]

Apple Skins

Whilst this recipe suggests peeling the apples to obtain a satisfactory stewed consistency, the content of phenolic compounds, dietary fibre, and minerals are higher in apple peel, compared to other edible parts of this fruit. Hence apple peel may be left on some of the slices to add additional benefits.[7]

Organic or Not?

Common questions arise relating to the growing methods employed and whether there is any benefit in choosing, where possible, to eat organically grown apples. Organic apples appear to have higher total phenolic content than integrated grown ones. Apples from organic production have also shown a higher content of hydroxycinnamic acids, flavanols, dihydrochalcones, quercetins and total phenolics than apples from integrated cultivation. [8]

The very high levels of phenolic compound in organically grown cultivars, and with it, its importance for human health leads to my recommendation to eat regional fruits from organic fruit growing instead of those grown under integrated cultivation. Sugar levels are also higher in organically grown cultivars making it a valid consideration for diabetics and the additional recommendation to include the herb cinnamon for its blood sugar managing benefits.[9]

However, both organic and non-organic apples display antigenotoxic potential by decreasing DNA damage after ingestion (Golden Delicious) and will still provide adequate phenols to aid immune maturation.[10]

Inflammation Control

> ***Apples through their polyphenolic compounds protect the intestinal tissues from inflammatory damage and cytokine activity via the management of a primary gene related amplifying component of immune defence called Nuclear Factor Kappa B (NFk-β) inhibition.***[11]

Serum C-Reactive Protein (CRP), a marker of acute inflammation levels have also been shown to have an inverse relationship with an intake of apples via flavonoid inhibition.[12]

Apples also aid immune regulation and diminish mucosal sensitivity via histamine suppression through reduction of mast cell degranulation. In addition they may be able to induce oral tolerance via inhibition of specialised tolerance inducing T cells (γδ T cell) degradation under allergen exposure in the gut.[13]

Brain Benefits

Apples also confer a benefit away from the GI Tract improving beta-adrenergic receptor physiology in the brain via down regulation of inflammatory cytokines.[14]

Sickness behaviour (an immune driven response characterised by malaise, fatigue, anhedonia, anxiety and depression) has also been beneficially mediated via mucosal tissue activation of T helper cell phenotype Treg and cytokine management, at a human dose equivalent of 3 apples per day.

> ***Soluble fibre, as derived from apples is resistant to digestion but fermentable. Fermentation of soluble fibre by GI bacteria (primarily in the ileum/colon) generates short-chain fatty acids (SCFAs). These SCFAs are described as two- to five-carbon weak acids, with butyrate appearing to have the greatest potential role in immunity due to its recently described palliative effect in inflammatory bowel diseases.*** [15]
> ***In part this appears due the improved quality of the epithelial barrier and diminished bacterial translocation and immune activation.***

Butyrate is a well recognised histone deacetylase inhibitor and transcription of certain cytokines appears reliant on acetylation of histones associated with their promoters. One way that diet could regulate the innate immune system is by changing T-helper (Th) cell polarisation and impacting T helper cell cytokine signalling ratios: Th 1/2 & Th17. These effector cell determining cytokines especially the anti-inflammatory IL-4 via suppression of IFN-γ then confer a greater state of immunological tolerance. The results in this trial showed

a neuroimmune benefit and faster recovery from lipopolysaccharide (LPS) induced sickness behaviour by up to 50% over the non-soluble fibre supported group in fact the non-soluble fibre had an inverse relationship with these effects.[16]

Prebiotic

A diet high in apples also has a direct impact on bacterial colonisation in the colon and may have benefits outside of immune management in the local tissues which in part is mediated by gene to gene interactions that includes altering genetic expression related to adiposity and so aids in weight management. It does this via bacterial gene expression changes associated with a favouring of Bacteroidetes growth promotion (a genus of bacteria found in abundance in normal weight humans and deficient in obese humans), and suggests a reduction in Lactobacillus species supplementation as supportive agents in this meal if weight management is a part of the desired outcome.[17]

Phenolic compounds found in apples as already described actually rely on bacterial species in the gut to modify them and so improve or otherwise their bioactive metabolites.[18]

The dihydroxylated phenolic acids derived from the microbial metabolism of apples present marked anti-inflammatory properties, providing additional information about the health benefits of dietary polyphenols and their potential value as therapeutic agents.[19]

> ***Apples also help to alter the pathobiont (these are commensals that alter their relationship with the host depending on environmental triggers) mix of bacteria in human guts when consumed regularly; suggesting a role for their use in mild to moderate dysbiosis induced inflammation and loss of tolerance.[20] In a small but clinically interesting study, healthy adults noted an increase in Bifidobacteria species and Lactobacillus numbers also rose, but Clostridium. Perfringens, Pseudomonas and Enterobacteriaceae declined on a diet of 2 apples a day for 2 weeks.[21]***

These findings indicate that apple consumption is related to an improved intestinal environment. Apple pectin is one of the effective apple components improving the faecal environment, citrus pectin produces a better total SCFA production in human gut than, soy, sugar beet, oat and pea fibre.[22]

Cinnamon

Cinnamon is added to the apples at the time of cooking as this herb has demonstrated a number of benefits to add value to the stewed apple.

Cinnamon inhibits experimental colitis by maturing antigen presenting dendritic cells into a tolerogenic format, increasing IL-10 production and TGFβ production whilst reducing IL-1, IFN-γ and TNFα. This suggests the potential of cinnamon extract as an anti-inflammatory

agent by targeting the generation of regulatory APCs and IL-10(+) regulatory T cells all of which contribute to the management of aberrant inflammation.[23]

Cinnamon also offers an insulin modifying role that helps to counteract the impact of consuming cooked apples (which increases the release of fruit sugars) providing access to this recipe by patients with metabolic syndrome and diabetes. The available in vitro and animal in vivo evidence suggests that cinnamon has anti-inflammatory, antimicrobial, antioxidant, antitumour, cardiovascular, cholesterol-lowering, and immunomodulatory effects. The use of cinnamon as an adjunct to the treatment of type 2 diabetes mellitus is the most promising area of research so far.[24]

Yoghurt

Yoghurt derived from cow's milk confers a number of potentially relevant immunomodulating effects in which suppression of cyclooxygenase 2 (COX2) proteins and lower pro-inflammatory cytokines feature.[25]

Yoghurt derived from soy may also offer immunomodulating properties depending on the cultures using during fermentation.[26]

Berries

Blueberries have been well studied to assess their effects in vivo and in vitro. Combining them with yogurt provides a synergistic effect that contributes to the suppression of colitis after just 9-10 days of ingestion.[27]

Arabinogalactans

Larch arabinogalactans are high molecular weight, highly branched, water-soluble polysaccharides, which contain units of D-galactose and L-arabinose and confer sweetness to the stewed apple whilst also providing mucosal immune activation. This includes natural killer cell (NKc) cytotoxicity and complement promotion both of which operate as part of the innate and adaptive immune systems. Other changes have been noted in anaerobe combinations – changes to the balance of bacteria in the gut - and ammonia reductions suggesting it has a role as a prebiotic as well.[28],[29]

Honey (Manuka)

Seeking to add additional bacterial modulating food ingredients may be done with Manuka Honey derived from New Zealand. This honey has shown potential in the treatment of antibiotic resistant organisms in the gastrointestinal tract.[30]

Almonds in Skins

Provide protein and immune modulating effects when consumed and their skins are intact.[31] Consumed as part of the dish they also provides a protein to carbohydrate ratio benefit

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