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Giang J, Lan X, Crichton M, Marx W, Marshall S. Efficacy and safety of biophenol-rich nutraceuticals in adults with inflammatory gastrointestinal diseases or irritable bowel syndrome: A systematic literature review and meta-analysis. Nutr Diet. 2021 May 7. doi: 10.1111/1747-0080.12672. Epub ahead of print. PMID: 33960587.

What We Know, Think We Know, or Are Starting to Know

Reading the title of this study, you may think "*I've never heard of biophenols.*" Neither had I. But you' ve definitely heard of 'polyphenols' , so let' s start out with a clarification on terms. The authors of the present paper correctly point out that the term 'polyphenol' implies phenolic compounds with two or more [hence 'poly'] phenolic rings [a type of chemical compound structure]. However, many phenolic compounds have a single phenolic ring, thus the authors state that the term 'biophenol' is a more accurate definition as it would include all plant-derived phenolic compounds.

There is, however, another accurate way of defining this group, which is to designate these compounds as (poly)phenols: all phenols are thus the operative term and the 'poly' in parentheses denotes that some compounds may have more than one phenolic ring [(1)]. (Poly) phenol is the term I personally prefer, because it is more recognisable, but as the present study used the obscure 'biophenols' , we shall stick with that for today.

Now, what of biophenols and the gut? Most of the evidence for gastrointestinal effects of biophenols has focused on their metabolism and absorption, and the generation of secondary metabolites by the intestinal microbiota [(1,2)]. It is now understood that there is only minor absorption of biophenols in the small intestine, and these compounds pass largely unabsorbed to the large intestine, where bacteria convert these biophenols into smaller metabolites, which are absorbed to the liver [(1,2)].

However, while the absorption and activity of biophenols in circulation has been a major focus of their potential protective effect in relation to cardiovascular and neurodegenerative conditions, it may be for the very fact biophenols are poorly absorbed that they influence gastrointestinal conditions. Biophenols, highly concentrated in the colon, may have direct contact with the mucosa and may have greater concentrations within the intestinal lumen than in systemic plasma circulation [(3)]. Biophenols exert a range of functions that have been characterised, influencing inflammatory signalling, immune signalling, and antioxidant defences [(1)]. Could this provide an underlying basis for benefit in gastrointestinal conditions? The present study investigated the effects of biophenol supplementation on gastrointestinal symptoms in Inflammatory Bowel Disease [IBD] and Irritable Bowel Syndrome [IBS].

The Study

The investigators conducted a systematic review of studies with the following inclusion criteria:

- Participants aged >18yrs
- With a condition of Ulcerative Colitis [UC], Crohn's Disease [CD], Symptomatic Uncomplicated Diverticular Disease [SUDD], or IBS
- Parallel or crossover design randomised controlled trials [RCTs]
- Intervention group using biophenol supplementation with no other therapy beyond routine standard care
- Biophenol supplement was listed on the Phenol Explorer database
- Control group of standard care alone or a placebo

The primary outcome was gastrointestinal symptoms [GIS], assessed subjectively in the included studies using condition-specific measurement tools. Secondary outcomes included inflammatory markers, oxidative stress markers, and adverse events. A meta-analysis of included studies was conducted in relation to the primary outcome of GIS. The standardised mean difference [SMD] was used to calculate effect sizes*: <0.4 was considered small, 0.4-0.7 was considered moderate, and >0.7 considered large.

*Geek Box: Standardised Mean Difference Measure of Effect

The standardised mean difference [SMD] of effect size is also known as Cohen's d [which we have come across in a previous Deepdive]. It compares two means: one from a treatment group and one from a control group or comparison group, and calculates an effect size by subtracting the effect in the placebo/control group from the effect in the intervention group, and dividing it by the pooled standard deviation of the groups. The difference between the SMD and a p-values is that the p-value simply tells you whether there is an effect that is statistically significant, while the SMD tells you the size of the effect, i.e., how much did the magnitude of effect in the treatment group differ to the magnitude of effect in the control group. Similar to the p-value being set at <0.05 for significant being arbitrary, interpreting the SMD results have been subject to similar classifications, and the general thresholds of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively. However, there is no accepted definition, and researchers may choose their own thresholds for effect size. The SMD may [and should] be accompanied with 95% confidence intervals, where the SMD value is the point estimate and the 95% CI provide the range for the potential effect size. This allows for comparison in effect sizes between studies. The effect size interpretation for the SMD is just a general guideline and - similar to the way in which a statistically insignificant finding does not mean 'there is no effect' - the relevance of a 'small' or 'large' effect size will depend on the exposure and specific context being studies. A Cohen's d of 0.4, for example, may be small-medium, but may represents a clinically meaningful difference.

Results: 23 RCTs were included, all of which were placebo-controlled. The sample sizes ranged from *n* = 16 to *n* = 189, and a total of *n* = 1556. 9 trials investigated IBD [7 with mild to moderate UC, 2 with mild to moderate CD], while the remaining 16 investigated IBS; there were no included studies on SUDD.

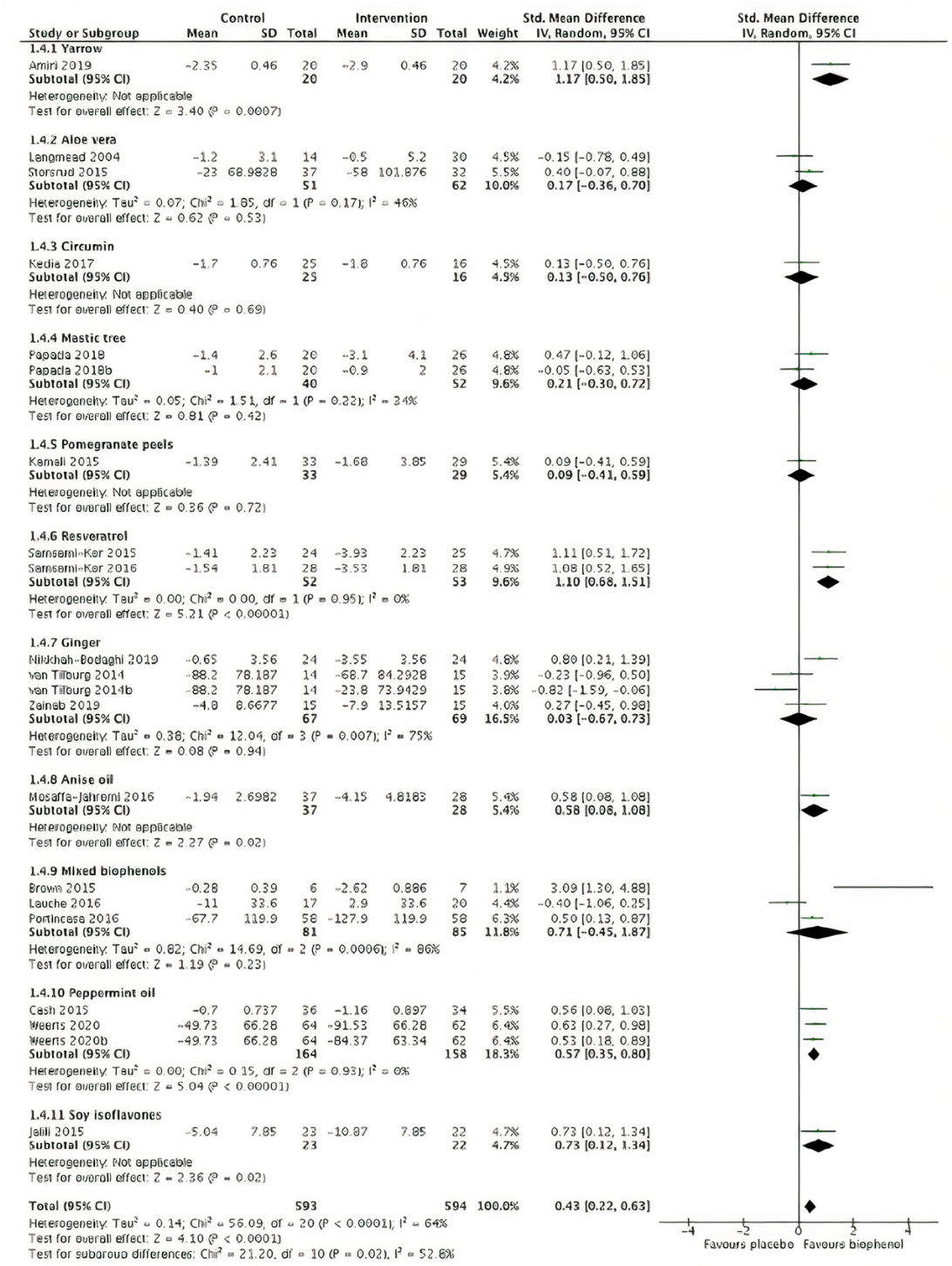
Systematic Review: 5 studies [all in IBS] investigated peppermint oil, 3 investigated ginger [2 IBS, 1 IBD], 2 investigated resveratrol [both in IBD], 2 used aloe vera [1 each IBS and IBD], 4 studies used mixed blends of two or more biophenols [all in IBS], while single studies investigated curcumin, wheatgrass, anise oil, soy isoflavones, mastic tree, yarrow, and pomegranate peel. The primary outcome of GIS were assessed using condition-specific tools, like scoring scales and disease severity indices. These differed from study to study, depending on the condition investigated.

Meta-Analysis: Compared to placebo, the overall meta-analysis for all 23 studies found that biophenol supplements resulted in a significant improvement in GIS with a moderate effect size [SMD 0.43, 95% CI 0.22 - 0.63]. The result did not differ by type of condition, IBS or IBD.

Subgroup analysis by type of biophenol supplement indicated that the both peppermint oil [moderate effect size SMD 0.57, 95% CI 0.35 - 0.80] and resveratrol [large effect size SMD 1.10, 95% CI 0.68 - 1.51] had the most significant effect compared to placebo. For the other supplements with two or more studies, there was no significant effect of aloe vera, mastic tree, ginger, and mixed biophenols.

4 studies in IBD assessed inflammatory markers, and found that interventions using mastic tree, resveratrol, yarrow, or aloe vera, cumulatively improved C-reactive protein by 1.6mg/L, compared to placebo. 2 studies in IBD also assessed an oxidative stress marker, malondialdehyde, and found a 1mmol/L improvement compared to placebo.

More adverse effects were noted in the intervention group vs. placebo groups, primarily gastrointestinal distress, although the differences between groups were not statistically significant, and did not differ by condition or type of supplement.



Forest plot *from the study of the meta-analysis of the different biophenol supplements.*

The Critical Breakdown

Pros: The inclusion criteria was clearly defined and relevant databases searched. The search included non-English language papers, if they could be translated. All included studies were RCTs [21 parallel arm, 2 crossover trials], and all were placebo controlled against an orally-consumed supplement in the treatment group. The results reported were thorough, including SMD and 95% CI, tests for heterogeneity, and sensitivity analyses according to type of condition, and type of biophenol supplement.

Cons: The certainty of evidence was assessed using the GRADE criteria, which has noted limitations for assessing nutrition studies [4]. Individual studies were mostly small sample sizes, and there was a wide array of supplemental interventions differing in type, dose, duration, and most likely phenolic composition. Given that studies were included only if the supplement was included on the Phenol Explorer database, not quantifying the content and levels of phenolic compounds in the respective supplements - given the wide range of products - was a missed opportunity. 'Gastrointestinal symptoms' is a broad, ill-defined outcomes, the assessment of which differs from study to study, and from condition to condition. The meta-analysis was a mesh of different exposures [more under ***Key Characteristic***, below].

Key Characteristic

A 1995 critique of meta-analysis stated that the emphasis on computing an overall effect size was "*a step in the right direction, but only if attention is paid to the conditions that must be fulfilled in order to make estimates applicable*" [5]. These conditions were homogeneity in study samples, intervention treatment, and outcomes, amongst others. The same author likened a meta-analysis which did not meet these conditions to comparing *"apples and killer whales"* in terms of study design [6], and the reality is that the present study meets all of the criticisms of meta-analysis in this context.

The rationale of meta-analysis is that pooling the results of trials, particularly if there are a number of trials with smaller effect sizes, can provide a more robust estimate of effect size. But how can the effect size be robust when what the treatment is [a wide array of biophenols differing in phenolic composition] is not even well defined beyond, in the words of the investigators, *"the general effect of biophenol-rich nutraceuticals"*? What does this even signify? What a meta-analysis provides in this context is a *"pseudo-quantitative answer where the conditions are often not yet ripe for such an answer to be meaningful."*

Interesting Finding

The benefit observed from resveratrol in the two studies included for IBD were both in patients with UC. Resveratrol has attracted research interest for its potential anti-carcinogenic and cardio-protective properties, however, it became clear that the observed protective effects in in vitro studies occur in dosage ranges not replicated in the human diet and only attainable pharmacologically [7]. However, this does not necessarily mean the same for gastrointestinal effects.

Resveratrol undergoes rapid metabolism, resulting in a high concentration of resveratrol metabolites, and these metabolites have been shown to adhere to epithelial cells in the gastrointestinal tract [8,9]. In a study investigating 500mg to 1,000mg supplemental resveratrol in patients with colorectal cancer, resveratrol metabolites were found to accumulate in colon tissue, resulting in decreased tumour cell proliferation [7]. The two studies on resveratrol supplementation in the present review used doses of 500mg/d, and while colorectal cancer and IBD are different disease, they share one unifying aspect of pathophysiology: inflammation [10,11]. The potential gastrointestinal effects of resveratrol warrant further investigation in this regard.

Relevance

If the aim of a meta-analysis is to provide applicable evidence, despite the finding in relation to effect size, the results are less actionable and meaningful when a general "biophenol-rich nutraceuticals improve IBD and/or IBS" is the conclusion, as offered in the Discussion. To quote Eysenck: *"The mean effect size...signifies what? It is an average of completely disparate methods, applied to completely disparate problems, with completely disparate controls."*

Studies on 11 different biophenol food supplements were included in this analysis, and it well established the composition of phenolic compounds varies widely from food to food [1,2]. While the overall effect size was positive, the subgroup analyses indicated that significant differences were primarily found for peppermint oil and resveratrol. All peppermint oil studies were in patients with IBS, while both resveratrol studies were in patients with IBD; this distinction is important because the conditions are entirely different and share no similarities in their respective pathophysiology.

The authors state that subgroup analysis showed no difference between IBD and IBS subjects in their perception of GIS, however, GIS was not assessed using the same tools as the subjective scales used are condition-specific. Therefore, it is difficult to say patient perception of GIS was not different when the measurement tools were assessing GIS in different ways, specific to either condition. Again, the pooled result here was an *"...average of completely disparate methods, applied to completely disparate problems..."*

Certain single studies - soy isoflavones, anise oil, and yarrow - yielded positive findings that contributed to the overall outcome in the meta-analysis, but all other biophenol supplement types had no significant effect. For the single studies included, it begs the question relevant to any meta-analysis: if multiple studies have to be added to give rise to a modest effect size, is it worth the effort and expense [5]? If you wanted to act on these findings as a practitioner, how would you go about selecting your 'general biophenol-rich nutraceutical' ?

In fact, the authors note themselves that the significant heterogeneity between studies means that the evidence is insufficient to determine dosing regimens. Put it this way: the study threw paint against a wall and it stuck, but the reader is invited to accept a general conclusion about the paint sticking, when the reader wants to know how to apply the paint properly, what colour, type, and amount of paint.

Application to Practice

Rather than sit with the general conclusion, let' s distinguish the primary significant findings from the subgroup analyses: peppermint oil in IBS and resveratrol in IBD. Peppermint oil is more established in IBS, and a number of meta-analyses have found a significant benefit to peppermint oil compared to placebo for reducing IBS symptoms [12,13]. The use of peppermint oil for IBS symptoms can be considered more reliable evidence. For resveratrol, there are plausible mechanisms for gastrointestinal effects and supporting mechanistic research in animal models [9,14]. The two studies included in the present analysis are, to date, the only human interventions for resveratrol in IBD; thus, the evidence is not quite there yet for a general recommendation for resveratrol supplementation in UC [14].

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