Release Notes 2022-08-01 : : I was going to drop vitamin D as a topic once I got the controversy note draft [18] out but this trial design was too funny and important to ignore. I won't have much time in next few days so releasing this today :) I'm interested in emulsifiers and absorption aids, currently have benzoate results queued up, like sorbitol but the anti-pathogen properties of dyes may be of larger significance. Once again I'm using developmental bibliography formatting code. It is not all that pretty but I'm finding wierd quirks as different sites reformat the submission so it is useful for debugging. The links should be live for now but the bibliography is supposed to preserve information if the links change. It is part of the TooBib [21] work which also should have turned the LinkedIn footnotes into better citations but they recently changed their page layout and I did not get back to this.

Live and Let Dye: A Confounding Factor in Vitamin D Data, Covid-19 Treatments and Everything Else ?

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(Dated: August 1, 2022)

Foods, drugs, and cosmetics are often formulated with ingredients to enhance the performance of active components. These components may improve physical properties, resistance to storage and environment, and appeal to consumers. They may be glibly considered inert in the absence of the active ingredients but this assumption needs to be considered when designing trials ostensibly evaluating the "active" ingredient. Dyes and absorption enhancers are two classes of common ingredients that may be active and confound the study of the intended ingredient. Dyes may have anti-pathogen properties that improve results in populations with significant infection rates among other effects. Absorption enhancers may be promiscuous or otherwise change nutrient profiles for host and other organisms beyond just the active ingredient similarly creating benefits or even detriment for afflicted patients. One important point is that no "thing" does just one thing but ingredients intended for these purposes may confound isolation of active ingredient effects. This is considered in the case of vitamin D formulations and possible interference in assessing it for covid-19 but the problem is pervasive.

I was recently exploring vitamin D controversies [18]. A related discussion on social media[1] brought to my attention a study in which vitamin D supplementation was shown to improve outcomes in covid-19 patients [24]. Results with vitamin D interventions for covid-19 have been mixed although some correlations or associations appear robust [18] so successful intervention trials create some curiosity. The authors appear to be giving Hidroferol to a treatment group but there is no indication of a placebo containing an identical vehicle- I may have missed it but this situation is quite common so worth consideration in any case. According to [3],

"Hidroferol contains ethanol, sorbitol (E-420) and sunset yellow (E-110)."

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[1] https://www.linkedin.com/in/jon-bergstrom-ph-d-61674a16/ https://www.linkedin.com/in/antonio-d-avolio-6b208240 https://www.linkedin.com/posts/antonio-d-avolio-6b208240_impaired-vitamin-d-metabolism-in-hospitalized-activity-6957581592735199232-Pix utm_source=linkedin_share&utm_medium=member_desktop_web https://www.linkedin.com/feed/update/urn:li:activity:6957581592735199232?commentUrn=urn:li:comment:(activity:A6957581592735199232,6958075248181211137),

While ethanol is listed as "1 percent" the total amounts of the other components is unclear. In this strength the vitamin D content is 266mcg and I would guess around 500mg or so for the vehicle. With no vehicle-only control group, the trial implicitly assumes that it is inert but a quick look at the assumption raises doubts about its role in this application. The individual components themselves are suspicious but even less predictable in combination.

Sorbitol itself is probably included to aid uptake but it is not selective for vitamin D. It has a history going back to at least 1959 as an arguable aid to B-12 absorption [11] [25], iron absorption [2], and is currently a concern for decreasing absorption of pharmaceuticals [13]. Even small amounts of sorbitol had to be suspected of improving availability of many nutrients especially with its ability to participate in deep eutectic solvent systems [9] . Sorbitol as a significant fraction of feed has been shown to improve livestock response to feed [10] at least in some animals [27]. Inconsistent effects could rely upon the mitigation or exacerbation of some unanticipated sporadic problem such as pathogen infection [5] or nutrient malabsorption. Sorbitol alone may even have activity similar to vitamin D as one work suggests sugars are associated with osteopetrosis and sorbitol has some calcium related functions [32].

Food dyes are a continuing source of safety controversy but often considered "inert" if they are not overtly dangerous. However, they typically have significant chemistry and biological activity particularly among the common azo dyes with planar ring systems. For example, sulfonated azo dyes as well as doxycycline were found to be selective inhibitors of "Suppressor of T cell receptor Signaling " in an interaction assisted by the rings of tryptophan or tyrosine [38]. Allergic reactions to drugs are often traced to the dyes [31]. It is so common that one case report identified it as a cause of serial adverse reactions to calcium supplements, carbamazepine, topiramate, phenytoin, levetiracetam after which the excipeients were suspected and confirmed as an allergy to sunset yellow [15]. Allergic reactions reflect immune modulation and would have to be considered in the host response to pathogens.

Many dyes types have antibiotic effects. Acridine for example is a decent antibiotic skeleton [35]. In 2018, Meng et al demonstrated activity against Human Enterovirus 71 in vitro and in mice with a variety of sulfonated azo dyes, including sunset yellow, via a several mechanisms [22]. Later work in 2021 suggested related dyes could increase infectivity [23]. Direct action of dyes on SARS-Cov-2 was investigated soon after it was identified. For example, diazo dye docking studies with SARS-Cov-2 [6] and a study of small molecule inhibitors directed only at SARS-Cov-2 Spike:ACE2 interaction [8] were described. The latter uses sunset yellow (FD and C Yellow 6) as a "negative control" on entry inhibition although it may show some effects below $100\mu M$ (figure 8 [8]). However, there is no reason to believe that "entry inhibition" is the only way it could have clinical relevance. Methylene blue has been directly investigated as an SARS-Cov-2 therapeutic [12] [14] with many possible virus and host directed mechanisms hypothesized.

Azo dyes are common in food and drugs with sunset yellow itself being quite common in drugs that may be used against SARS-Cov-2 . At least one formulation of azutrhomycin contains FD&C Yellow 6 [1] The amount of dye in commercial products such as drugs and supplements is not public but some measurements have been made and 1mg/tablet would not be unrealistic [16]. Its worth noting however that significant amounts may be in common snacks [29] which should effect all arms equally but may vary significantly with age and culture. Sunset yellow has a molecular weight of 452.4. One milligram is then about 2.2 micromoles. Dissolved in 1 liter of stomach contents then micromolar concentrations may be transiently possible with localized higher ones. There is some possibility that at lower concentrations sunset yellow could have impact on relevant pathogens. The work on in vitro and in mice azo dye experiments with EV-71 indicated that E-151 (Brilliant Black) inhibitory concentrations were around , " 2.39μM to 28.12μM, whereas its 50% cytotoxic concentration was $1{,}870\mu$M", leading the authors to speculate that 1-5mg/kg/day of E-151 may have significant clinical benefit [22]. Mice receiving 200mg/kg/day uniformly survive an EV-71 challenge. Sunset yellow had a higher inhibitory concentration under these conditions and was not investigated as thoroughly as the superlative dyes.

Covid-19 is generally attributed to or defined by SARS-Cov-2 . However, interactions with other pathogens have been described. Debate over the efficacy of Ivermectin identified efficacy against covid-19 due to elimination of parasites as expected of the drug with no efficacy "where strongyloidiasis was not endemic" [7]. It is usually considered as a respiratory disease although a GI component exists [37] and is currently of unknown significance [28] [36]. Bloodstream infections with GI organisms may be one concern [33]. The fact that one formulation component had activity against any GI pathogen is itself cause for interest. Direct activity against any part of the SARS-Cov-2 lifecycle is not necessary to change a clinical outcome. Therefore, it is difficult to be confident that any clinical response is due to the intended drug or an excipient or some interaction. covid-19 also has steep robust age-severity curve. As chronological age per se is not likely a factor, age-related host changes have to be suspected as mediators. These have variously been considered as immunological and nutritional changes[20]. Observed or suspected changes to both may occur from the combination of ingredients included discussed here. Pathogen virulence and clinical relevance may be an inducible phenotype so changes in nutrient availability could have a clinical impact.

Mitigation of a subclinical risk factor for severe covid-19 is still important to the patient but improvement will only be observed in the population with this unseen risk factor. Infectious causes of other diseases such as the earlier case of ulcer [30] and more recently Alzheimer's Disease [4] [34] are becoming better accepted. Awareness of virulence

modulation from components such as this may help resolve contemporary debates and lead to better solutions. The combination of dye with an uptake modifier is probably not safely assumed to be neutral towards pathogens or the patient's immune status. Indeed, modified uptake due to sorbitol may alter any IC_{50} significantly.

If you absolutely insist that "X is a Y and does Z" then it is easy to miss problems like this (unpublished personal notes [19]) . However, consideration of all aspects of each ingredient may avoid misleading interpretations. In any case, it is important to consider the vehicle as potentially live and consider it as at least one control arm. This may be a particular problem with vitamin D but if dyes and other formulation components are active against pathogens it could be much more widespread. Apparent benefit would only be seen in populations with a susceptible clinically relevant organism or a specific immune status leading to inconsistent and confusing results.

Nutrient uptake, particularly of lipophilic nutrients or those with variable solubility and stability may be an unappreciated issue with aging. Particular components that get around those problems may be covert contributors to clinical effects. Sorbitol and dye may be one combination but I have also explored benzoate and silver for uptake and anti-pathogen effects [17]. It is possible that unappreciated interactions in natural food are also important.

I had earlier thought that the better controlled vitamin D trials were less successful and this is an example with questionable control but one that can be cited as a vitamin D success. Careful review of clinical trials for placebo among other issues may clarify roles for confounding formulation components.

Placebo matters and " a p-value is no substitute for a brain."[26]

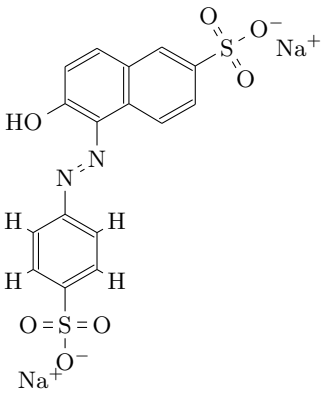

FIG. 1: Stucture of Sunset Yellow or FD and C yellow 6

1. SUPPLEMENTAL INFORMATION

1.1. Computer Code

2. BIBLIOGRAPHY

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1. Pubmed eutils facilities and the basic research it provides.

2. Free software including Linux, R, LaTex etc.

3. Thanks everyone who contributed incidental support.

Appendix A: Statement of Conflicts

No specific funding was used in this effort and there are no relationships with others that could create a conflict of interest. I would like to develop these ideas further and have obvious bias towards making them appear successful. Barbara Cade, the dog owner, has worked in the pet food industry but this does not likely create a conflict. We have no interest in the makers of any of the products named in this work.

Appendix B: About the Authors and Facility

This work was performed at a dog rescue run by Barbara Cade and housed in rural Georgia. The author of this report ,Mike Marchywka, has a background in electrical engineering and has done extensive research using free online literature sources. I hope to find additional people interested in critically examining the results and verify that they can be reproduced effectively to treat other dogs.

Appendix C: Symbols, Abbreviations and Colloquialisms

TERM definition and meaning

Appendix D: General caveats and disclaimer

This document was created in the hope it will be interesting to someone including me by providing information about some topic that may include personal experience or a literature review or description of a speculative theory or idea. There is no assurance that the content of this work will be useful for any paricular purpose.

All statements in this document were true to the best of my knowledge at the time they were made and every attempt is made to assure they are not misleading or confusing. However, information provided by others and observations that can be manipulated by unknown causes ("gaslighting") may be misleading. Any use of this information should be preceded by validation including replication where feasible. Errors may enter into the final work at every step from conception and research to final editing.

Documents labelled "NOTES" or "not public" contain substantial informal or speculative content that may be terse and poorly edited or even sarcastic or profane. Documents labelled as "public" have generally been edited to be more coherent but probably have not been reviewed or proof read.

Generally non-public documents are labelled as such to avoid confusion and embarassment and should be read with that understanding.

Appendix E: Citing this as a tech report or white paper

Note: This is mostly manually entered and not assured to be error free.
This is tech report MJM-2022-011.

Version	Date	Comments
0.01	2022-07-28	Create from empty.tex template
0.50	2022-08-01	release due to time constraint MJM-2022-011
-	August 1, 2022	version 0.50 MJM-2022-011
1.0	20xx-xx-xx	First revision for distribution

Released versions,
build script needs to include empty releases.tex

Version	Date	URL
0.50	2022-08-01	https://www.linkedin.com/posts/marchywka_role-of-excipients-in-vitamin-d-other-trials-activity-69599
0.50	2022-08-01	https://www.researchgate.net/publication/362404794_Live_and_Let_Dye_A_Confounding_Factor_in_Vitamin_D
0.50	2022-08-01	https://www.academia.edu/s/147a7d3c42
0.50	2022-08-01	https://zenodo.org/record/6950305#.YugybnXMJCU

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}

Supporting files. Note that some dates,sizes, and md5's will change as this is rebuilt.

This really needs to include the data analysis code but right now it is auto generated picking up things from prior build in many cases

```
3471 Aug 1 15:45 comment.cut d72314ca3e59e6b7b7503750d96ef35b
6146 Aug 1 15:45 dye.aux cf640d7ade54e5f761b08f114588c981
21226 Aug 1 15:45 dye.bbl fc2682d9947944bcfbe509bd4ae60fd5
142734 Aug 1 15:45 dye.bib 47dd39f1397a0f47bd884f5938e1c406
2186 Aug 1 15:45 dye.blg ac1fdf7e11ec2c1f5d51bbbed8438d11
0 Aug 1 15:51 dye.bundle_checksums d41d8cd98f00b204e9800998ecf8427e
30142 Aug 1 15:45 dye.fls 7778d223856f2b111476682dba6f7544
2 Aug 1 15:45 dye.last_page c30f7472766d25af1dc80b3ffc9a58c7
60867 Aug 1 15:45 dye.log 410876a21d9157b5d41b1037f615359a
616 Aug 1 15:45 dye.out 58842cfbc062d69121c094a77cc098c6
235540 Aug 1 15:45 dye.pdf f36e83f447e7618d8b7c4572b33330ae
28309 Aug 1 15:45 dye.tex 627c967592c4c54f70827060f0f5fd0d
631 Jul 30 03:55 fdc6yellow.tex 940fbf16cd81148f62f644b24f45d771
31664 Jul 28 12:20 /home/documents/latex/bib/mjm_tr.bib a4084ce9fec8fbcf3611f3b37c06d8ba
33603 Aug 1 09:36 /home/documents/latex/bib/releases.bib 254d2dea802b21bae0b967eda66e27b4
7331 Jan 24 2019 /home/documents/latex/pkg/fltpage.sty 73b3a2493ca297ef0d59d6c1b921684b
7434 Oct 21 1999 /home/documents/latex/pkg/lgrind.sty ea74beead1aa2b711ec2669ba60562c3
7162 Nov 13 2015 /home/documents/latex/pkg/mol2chemfig.sty f5a8b1719cee30a4df0739275ac75f8a
1069 Oct 15 2021 /home/documents/latex/share/includes/disclaimer-gaslight.tex 94142
    bbe063984d082bff3b400abe0fb
425 Oct 11 2020 /home/documents/latex/share/includes/disclaimer-status.tex b276f09e06a3a9114f927e4199f379f7
1478 May 14 09:24 /home/documents/latex/share/includes/mjmaddbib.tex cb57cbf8cd5c5ac8f44c98b34ba9227a
122 Jun 27 18:37 /home/documents/latex/share/includes/mjmlistings.tex 439aab9f9b760c03d4278a11e1a03079
3867 Jun 27 18:32 /home/documents/latex/share/includes/mycommands.tex 3d3fa863325a59409782f4a82a3e618e
2901 Jun 17 2020 /home/documents/latex/share/includes/myskeletonpackages.tex
    fcfcd2e3c8d69d533932edaaa47f53a1
1538 Aug 14 2021 /home/documents/latex/share/includes/recent_template.tex 49763d2c29f74e4b54fa53b25c2cc439
940 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/cmextra/cmex7.tfm
    f9e66c0105a30e64e3a0f5c4f79efb8d
852 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msam10.tfm
    b4a46d2c220ee4ffaaf87c608f8593cd
860 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msam5.tfm
    c4142ffef6136ff95621fbe99efb7cec
864 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msam7.tfm 2998
```

```
    d813a00ebf21070684f214a50f7e
844 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msbm10.tfm
    f7721eee07bdc9e743e6c5f3f7e3d06d
876 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msbm5.tfm 9
    e3df3efef7afc4b0381e88a6402f777
876 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msbm7.tfm 374365713297
    d597717720c5786882e5
1260 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmbx12.tfm 41596a2c763cf972bbdd853b378ec55a
1264 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmbx9.tfm c3f8c3f0292777e1e9153581c59f8506
928 Jul 23 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmex10.tfm 0086317ff95b96ceb2bce0f96985e044
1464 Jul 23 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmmi10.tfm 9178465cbc6627ccd42a065dd4f917b7
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1464 Jul 23 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmmi7.tfm 2b1ed046f0a24d705b439f2ed4b18786
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1224 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmr12.tfm 48d5728dc6473917c0e45f34e6a0e9cd
1156 Jul 23 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmr5.tfm 19157dffae90ad9aaaed44f08b843218
1236 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmr6.tfm 63e3c1344d1e22a058a5cb87731337e0
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1228 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmr8.tfm 29a15bf51bfb16348a5cabb3215cf3fd
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1056 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmsy8.tfm 7ef80e56d3b9e223d3bce5a9065b95ad
116813 Aug 1 15:09 non_pmc_dye.bib 66d530ef7073e4423b59ad1fd270f135
25538 Aug 1 13:51 pmc_dye.bib 8180491418b764c28353e7efde92d5e3
413 Jul 28 12:20 releases.tex 56213b8bd7e164dd6e668b62f5acf868
31050 Jul 21 2011 /usr/share/texlive/texmf-dist/bibtex/bst/urlbst/plainurl.bst
    ffdaefb09013f5fd4b31e485c13933c1
1293990 Jul 23 2019 /var/lib/texmf/web2c/luatex/lualatex.fmt 0fdf3dce2c9cd956e421c2c52037b3cc
235540 Aug 1 15:45 dye.pdf f36e83f447e7618d8b7c4572b33330ae
```