

Author's response to reviews

Title: GFS, a preparation of Tasmanian *Undaria pinnatifida* is associated with healing and inhibition of reactivation of Herpes

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PDF covering letter

Reviewer's report

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Reviewer: Dr Jane Teas

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication:

Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

Discretionary revisions

None

Compulsory revisions

1. The first time ACV is used in paragraph 1 it should be preceded by Acyclovir with ACV in parentheses.

- Altered

2. Herpes appears in the text as both Herpes and herpes. There should be consistency. Likewise, anti viral or anti-viral should be used consistently throughout the paper.

Altered

3. In the second paragraph, "including a heparin sulphate receptor" appears but the importance of this type of receptor is unclear in relationship to seaweed. More information needs to be provided to the reader at this point.

This has been included

4. Under "Materials and methods", p. 4, GFS is not defined, nor is there any indication of quality control in the preparation.

GFS is now defined

5. Under "Patient study", it is confusing to have 17 patients in total, if 15 of those 17 had active infections, and 6 had latent infections. Does this mean that 2 patients had only latent infections, and 4 had both active and latent infections?

In order to reduce confusion, an explanatory note is now included in the text. Of the 17, 15 were treated initially for an active infection. Four of these continued to take a lower dose after the active infection cleared up. A further two people who did not have active infection, but expected to have one as a result of their past experience, also took GFS.

6. Under "In vitro effects on HSV" (p4) it seems that the stock solution (p.5) was made from dried seaweed and distilled water (?), and that it was in a 2.5 mg/ml solution. Was it then refrigerated (the authors state that it was a "stock" solution, but was it made just for their one experiment?).

The preparation was made from the seaweed and water, and dried down, and then retaken into water at 2.5mg/ml. The term 'stock' is simply a term for the most concentrated solution.

7. Where were the laboratory strains of HSV and HCMV obtained?

From the ATCC, at Ken Thompson laboratories.

8. Under "T cell stimulation in vitro", where were the human blood samples obtained? Were they from healthy subjects? From several subjects or just one?

From pooled healthy subjects.

9. Since the ConA and the PHA were added at 1 mcg/ml, and the GFS solution was added at 25 mcg/ml, was this a fair comparison? Or did the 25 mcg/ml from a 2.5 mg/ml stock solution become 1% which made it 1 mcg/ml? This section needs to be clarified.

The comparison is between 25mcg/ml of the Undaria crude extract and 1mcg/ml of the pure Con A.

10. Under "Patient Study", the listing of patients and their types of Herpes infections should be included under "Patient study" in the Methods section.

OK

11. Under "Active Infection" it is unclear what "relief from symptoms" means. Does it mean drying of lesions, lessening of pain, disappearance of lesions, or disappearance with no recurrence?

Relief from Symptoms was where patients reported what was, for them, a significant lessening of their symptoms. The wording now reads "significant lessening or disappearance"

12. In the second paragraph, what does "noncompliant dosage" mean? How noncompliant were these two patients? And why were they noncompliant? Was it difficult to take the capsules, did they forget, or did it make them feel bad when they took the capsules?

They did not take the capsules regularly, but sporadically, when they remembered. No reports of difficulty in taking the capsules were noted.

13. In the 4th paragraph under "Active infection" the subjective results of 2 patients are described. What happened to the third case of Herpes zoster?

The section has been revised

14. Under "Latent infections", 4th paragraph, it is unclear whether these two female patients would have expected an outbreak during the one month of GFS. Why did these patients not continue taking the GFS if it worked so well to prevent HSV-2 outbreaks?

The patients has experienced regular outbreaks of HSV (at least one a month), and were thus taking the GFS to assess its effects. The reports were up to date the paper was written. These patients continued to take GFS after this time.

15. P.6, first paragraph: why was a low grade persistent Herpes zoster called "latent" if the patient had lesions of the whole torso? It would seem like it was active. Also, did the lesions recur when the GFS was stopped?

Unknown patient was still taking it at the time this was written. Replaced with 'recurrent'.

16. Under "In vitro effects on HSV" it would be helpful if there were more description of Table 2. It would also be helpful to know what Acyclovir would do under the same laboratory conditions with these same

Further details have been added to this section, including references to in vitro work reported at conference on clinical strains, including ACV resistant strains.

17. Under "Discussion" it is hard to know what "increased rate of healing" means. It would be helpful to have an estimate of normal healing or duration of active lesions was thought to be for each of the treated patients. Additional columns in Tables 1A and 1B could provide this information.

Lesions are commonly considered to last 10 days in the case of HSVI and II, although the time course of outbreaks differs between patients, and between each active infection. This information was not available from the shingles sufferers.

18. In the last paragraph on page 6, the discussion adds new results rather than discusses the results of this study with those of other published studies. The addition of information about HIV seems unsubstantiated. How similar are the cell surface receptors for HSV and HIV?

Information regarding HIV removed.

19. In the next paragraph on p. 7, it would be helpful to summarize the findings of Shan.

Taken into account

20. In the next paragraph, it is unclear why inhibition of viral infection of mucosal surfaces of the gut would affect skin lesions. Is Herpes thought to be spread by ingestion? Or is this paragraph suggesting a route for oral absorption of GFS that would account for the immune stimulation that is thought to inhibit the Herpes skin lesions?

This section has been altered to take the above comment into account.

22. In Tables 1A and 1B, it would be helpful to know how long the course of GFS was, the normal length of the Herpes-related symptoms, the symptoms of the outbreak, and the length of time with GFS supplementation for resolution.

The normal length of symptoms has been introduced into paragraphs in the methods sections.

23. This paper describes a non-toxic approach to treating Herpes infections, and could potentially be of great value to people who suffer from chronic Herpes. It might be more helpful to describe a smaller set of HSV patients in greater detail. It would also be helpful to know how the dose of GFS was chosen. Does it reflect the average Undaria intake in Japan, where there is a reduced (by how much?) incidence of HSV? It is an intriguing idea that a common dietary food in Japan could be acting like a Herpes inhibitor. Seaweed as an anti-viral nutraceutical is very interesting.

The dose was chosen on the basis of it being within a normal dietary range for Japan. The incidence of HSV data is now in the text in the introduction.

