Reviewer’s report

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

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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 preceeded by Acyclovir with ACV in parentheses.

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.

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.

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

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?

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?).

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

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.

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

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?

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?

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?

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?

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?

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 virus 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.

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?

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

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?

21. 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.
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 nutriceutical is very interesting.

**Competing interests:**

None declared.