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Immune Support for Clients with Kidney Transplants

The purpose of this paper is to explore immune support for clients with kidney transplants who are on long-term immunosuppressive medications. Unless the donor is an identical twin, a person who receives a kidney transplant will need to take maintenance immunosuppressants throughout their lives to stop their immune system from rejecting the kidney. As these medications lower immune function, they increase the risk of infection from other pathogens. This reduction in immune function is dose-dependent, with lower maintenance doses having less side effects than stronger induction immunosuppressants used at the time of transplant.[1]

Doctors generally recommend that people with kidney transplants don't take any supplements or herbal products that support the immune system without discussing them with their doctors, because any increase in immune function could lead to a risk of transplant rejection.[2] In this paper, I explore how to support clients concerned about their risk of developing infectious diseases such as SARS-CoV-2, without risking transplant rejection. Specifically, I am looking at the concurrent use of two related compounds, the immunosuppressant drug cyclosporine and the immunomodulatory and nephroprotective fungus cordyceps.

Cyclosporine is an immunosuppressant drug used in solid organ and bone marrow transplants, as well as for autoimmune and inflammatory conditions including atopic dermatitis, systemic lupus erythematosus, and rheumatoid arthritis. It is isolated from the *Beauveria nivea* fungus,[3] a parasitic fungus in the Cordycipitaceae family that is closely related to the medicinal mushroom *Cordyceps militaris*, a traditional Sikkim immunomodulant.[4]

Cyclosporine is in the class of drugs known as calcineurin inhibitors, which inhibit the enzyme calcineurin, and thus inhibit T-cell activation. Its main immunosuppressive effect is inhibiting the production of interleukin-2. It is metabolized primarily by the enzymes CYP3A4 and CYP3A5, with some potential metabolism by CYP3A7 enzymes. Though it has about 25 different metabolites, it is not a pro-drug, but it is a P-gp substrate. It is primarily excreted through the bile with 3-6% excreted through the urine.[5]

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[1] *Immunosuppressants*. (2015, December 24). National Kidney Foundation. https://www.kidney.org/atoz/content/immuno
[2] Borchard, M. (2021, December 21). [Phone call].
[3] *Cyclosporine*. (n.d.). Retrieved December 23, 2021, from https://go.drugbank.com/drugs/DB00091
[4] Panda, A. K., & Swain, K. C. (2011). Traditional uses and medicinal potential of Cordyceps sinensis of Sikkim. *Journal of Ayurveda and Integrative Medicine*, *2*(1), 9–13. https://doi.org/10.4103/0975-9476.78183
[5] *Cyclosporine*. (n.d.).

Cyclosporine has a narrow therapeutic range, and its immunosuppressive effects are life saving in people with solid organ transplants.[6] Missing even a single dose can increase the likelihood of transplant rejection.[7] It is contraindicated with many other medications due to its CYP3A4 inhibitory effects, its narrow therapeutic window, and its risk of nephrotoxicity and ototoxicity.[8]

Cordyceps sinensis is a combination of caterpillar and the fungus that grows on it found at high altitudes in Sikkim. It has been used as a tonic by traditional Sikkim healers to support energy levels, stamina, libido, and immunity.[9] *Cordyceps militaris* can be cultivated, and thus is a much more sustainable medicine, with very similar constituents.[10]

In principle, immunostimulatory herbs should not be used along with immunosuppressant medications, especially in a situation as high risk as a kidney transplant, due to the concern that they might counter the immunosuppressant effects and thus risk causing transplant rejection. However, *Cordyceps* spp. is not only an immunostimulant but also an immunomodulant and a nephroprotective. It is used in China in hospitals that practice Chinese medicine as an adjunct immunomodulant along with cyclosporine to lower the dose and as a nephroprotective to ameliorate side effects. In a clinical trial with 69 people with kidney transplants, 3g of *Cordyceps sinensis* in conjunction with cyclosporine was found to protect against cyclosporine-induced nephrotoxicity, with no adverse effects reported. [11] The study was only 15 days, but the concentrations of cyclosporine in the blood remained constant and the markers of nephrotoxicity, as indicated by serum creatinine and blood urea nitrogen levels, decreased over the 15 days.

A Cochrane systematic review was completed in 2015 to assess the use of cordyceps as an adjunct therapy to cyclosporine in people with kidney transplants. In four of the studies in the review, cordyceps was compared with azathioprine (AZA), and in one study, cordyceps plus low dose cyclosporine was compared to standard dose cyclosporine. The potential mechanisms of action of cordyceps that this review found were its immunomodulatory effects - both stimulating and suppressing and its antioxidant and antiinflammatory activity. Cordyceps compared with AZA was found to reduce incidence of infection, anemia and leukopenia, and improve liver and kidney function, without significant changes in survival of kidney or host, or graft rejection.

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[6] Colombo, D., Lunardon, L., & Bellia, G. (2014). Cyclosporine and Herbal Supplement Interactions. *Journal of Toxicology*, *2014*, 145325. https://doi.org/10.1155/2014/145325
[7] *Immunosuppressants*. (2015, December 24).
[8] *Neoral, Sandimmune (cyclosporine) dosing, indications, interactions, adverse effects and more*. (n.d.). Retrieved December 24, 2021, from https://reference.medscape.com/drug/neoral-sandimmune-cyclosporine-343196#3
[9] Panda, A. K., & Swain, K. C. (2011).
[10] Yu, H. M., Wang, B.-S., Huang, S. C., & Duh, P.-D. (2006). Comparison of Protective Effects between Cultured *Cordyceps militaris* and Natural *Cordyceps sinensis* against Oxidative Damage. *Journal of Agricultural and Food Chemistry*, *54*(8), 3132–3138. https://doi.org/10.1021/jf053111w
[11] Xu, F., Huang, J. B., Jiang, L., Xu, J., & Mi, J. (1995). Amelioration of cyclosporin nephrotoxicity by Cordyceps sinensis in kidney-transplanted recipients. Nephrology Dialysis Transplantation, 10(1), 142–143. https://doi.org/10.1093/oxfordjournals.ndt.a090842

Cordyceps plus low dose cyclosporine was found to improve albumin and uric acid levels and lower the rates of lung infection as compared to standard dose cyclosporine, without impacting kidney function or rejection, or survival of kidney or host. The cordyceps group also experienced less kidney and liver damage, possibly due to the lowered cyclosporine dose. While these results are extremely favorable, the review was limited by size (447 participants total) and duration of the studies included.[12] Longer-term studies would provide more robust evidence that could lead to the use of cordyceps outside of a Chinese medicine context.

There are no clinical trials in Pubmed specifically focused on using cordyceps to boost the immune system for transplant recipients, though the studies in the Cochrine review above noted the immune boost as a positive side effect of its use to reduce transplant rejection or nephrotoxicity. Outside the realm of transplants, however, cordyceps has been studied as a potent immunostimulant. *Cordyceps* spp. has been shown to promote the innate immune system in acute respiratory infections in humans and the adaptive immune system, both cellular and humoral, in mice.[13] In Chinese medicine *Cordyceps sinensis* is used to enrich the Lung Yin and Yang. The Lungs are the organ most connected to the outside world, and for this reason, cordyceps is used in Chinese medicine to prevent infections, colds, and flus, and to treat SARS.[14]

Practically, because cordyceps interacts with the immune system, a client's nephrologist would need to be a part of the conversation, and the likelihood is small that they would be open to herbal immunostimulants of any kind, regardless of the research. This hesitancy is reasonable, because the survival of the kidney is at stake. As a beginning clinical herbalist, I would not feel comfortable recommending cordyceps for use along with cyclosporine for a kidney transplant patient without learning alongside experienced practitioners who have used it successfully, and even then, only with clear client interest and communication and if their transplant was very stable. Additionally, almost all people with kidney transplants are on many different immunosuppressant medications[15], which may all interact with each other and with cordyceps, so the specific combination of medications would need to be thoroughly researched.

The safest strategies to support a client's immune system when polypharmacy is involved are nutritional strategies. Food quantities of aromatic vegetables including alliums, horseradish, and chili peppers can break up mucus. Orange, carotenoid-containing vegetables contain vitamin A and support mucus production. Including dietary sources of zinc and vitamin D can build

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[12] Hong, T., Zhang, M., & Fan, J. (2015). *Cordyceps sinensis* (a traditional Chinese medicine) for kidney transplant recipients. *Cochrane Database of Systematic Reviews*, *10*. https://doi.org/10.1002/14651858.cd009698.pub2

[13] Lin, B. Q., & Li, S. P. (2011). Cordyceps as an herbal drug. *Herbal medicine: biomolecular and clinical aspects*, *5*.

[14] Chiu, C.-P., Hwang, T.-L., Chan, Y., El-Shazly, M., Wu, T.-Y., Lo, I.-W., Hsu, Y.-M., Lai, K.-H., Hou, M.-F., Yuan, S.-S., Chang, F.-R., & Wu, Y.-C. (2016). Research and development of Cordyceps in Taiwan. *Food Science and Human Wellness*, *5*(4), 177–185. https://doi.org/10.1016/j.fshw.2016.08.001

[15] *Immunosuppressants*. (2015, December 24).

immunity long-term. Fermented foods help keep the microbiome populated, supporting the immune system in countless ways.[16] And besides grapefruit,[17] foods are generally considered safe for clients with kidney transplants to experiment with and enjoy.

[16] Bancroft, Betzy. “Food Support for Health Conditions.” Food as Medicine. Vermont Center for Integrative Herbalism (VCIH). Vermont, Plainfield. 4 November 2020. Lecture.
[17] Borchard, M. (2021, December 21).