2015

Feasibility of Integrating Tripterygium wilfordii into Modern Cancer Therapy for Increased Efficacy and Minimal Toxicity

Ngoc T. Vo
Virginia Commonwealth University, vont2@vcu.edu

Feasibility of Integrating *T. wilfordii* into Modern Cancer Therapy for Increased Efficacy and Minimal Toxicity

Ngoc Vo, Biomedical Engineering – Prof. Mary Boyes, VCU Honors College

Introduction

- Diseases are becoming more resistance to the drugs that be used in the market today. Current solution to such problems is to develop strong and more powerful drugs to combat the disease.
- However, accompanying these powerful drugs are adverse side effects that is proportional to the effectiveness of the drug.
- According to the CDC, cancer is the second leading cause of death in the U.S, and the American Cancer Society reported that millions of new cancer cases are being diagnosed each year.
  - Current cancer treatments are chemotherapy and ionizing radiation.
  - Adverse effects are hair loss, extraneous damage to healthy cells, decreased immunity, etc.
  - In order to find alternative treatment methods with less side effects, we turn to Eastern medicine.

Table 1. Eastern Medicine vs. Western Medicine

Medical View	Chinese	Western
Diagnosis/Treatment	Philosophic	Scientific
Clinical Distinction	Wholeness	Local
Medicine	Natural	Chemical
Study Method	Human Experience	Clinical Lab testing
Preventive View	Preventive	Sanitary
Treatment methods	Individualised	Standardised
Treatment Goals	" Cure" oriented	Reduction of symptoms
Treatment Views	Natural	Invasive

Note: From “Consumers’ Perceptions of Chinese Vs. Western Medicine” by Piron, F., Ching, C., Peng, E., Ching, H., 2000, *Advances in Consumer Research, 27*.

- *Tripterygium wilfordii*, an herbal medicine traditionally used to treat inflammation in China, contains compounds (triptolide and celastrol) that prevent the growth of solid tumors, induce apoptosis, and prevent metastasis of developed tumors.
- Studies of triptolide and celastrol on various cancer cells lines (*in vitro* and *in vivo*) have revealed some information about their mechanism (mode of action) and toxicity.

Figure 1. *T. wilfordii* (雷公藤, *lei gong teng*; “thunder god vine”)

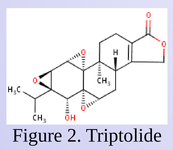

Figure 2. Triptolide ($C_{20}H_{24}O_6$; MW: 360.404)

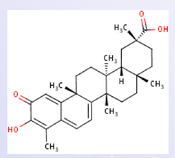

Figure 3. Celastrol ($C_{29}H_{38}O_4$; MW: 450.6152)

Findings

Therapeutic Effects of Triptolide

- Inhibits growth of 4 solid tumors (B16 mouse melanoma, MDA-435 human breast cancer, TSU bladder cancer, and MGC80-3 gastric cancer). Individual effects varies between cell lines, showing cell specificity (Yang et al.).
- Kiviharju et al. had similar results when studying triptolide in prostatic epithelial tumors.
- Inhibit vessel formation by nearly 50% at 1.2 μM (He et al.).
- Yang et al. also found that after 3 days of treatment, there was a significant reduction in proteins and molecules for cell cycle progress.
- Kiviharju et al. found similar results in prostatic cancer cells. Triptolide increased apoptosis rate slightly after 24h and significantly after 48h.

Therapeutic Effects of Celastrol

- Celastrol cause cell cycle arrest at low concentration and quickly induce apoptosis at higher concentrations above 800 nM (Peng et al.).
- Peng et al. also found that celastrol increased numbers of cell in G0/G1 starting at concentration of 400 nM.
- Celastrol inhibits VEGF in HUVECs cells at concentration of 1-2 μM (Pang et al.).

Synergy

- Other studies have also found that triptolide and celastrol can potentiate the effects of current cancer treatment (chemotherapy and IR) at low dosages, thus lessening the adverse effects.

Toxicity & Adverse Effects

- Triptolide causes “severe toxicities towards the gastrointestinal, renal, cardiac, hepatic, hematopoietic, and reproductive systems” (Liu et al.).
- No adverse reactions have been found to be associated with celastrol.

Conclusion

- Potent drugs are being developed to combat diseases with growing resistance for current prescription, and adverse effects induced are proportional to strength of drug.
- The approach taken to rectify this problem is to look for alternative treatment methods in Eastern medicine. This study is conducted on *T. wilfordii* and its anti-cancer effects.
- The bioactive compounds within the plant roots have demonstrated strong anti-cancer effects, but they can induce detrimental side effects.
- Proposed solution is to use a crude extract of the roots as a treatment for cancer.
- If the results are undesirable, then research should be taken in the direction of producing combination drugs containing triptolide and/or celastrol with selected non-bioactive compounds in the plant.

Proposed Solution

Hypothesis:
Since *T. wilfordii* is not known to induce the multitude of adverse effects that triptolide and celastrol has and yet still contains triptolide and celastrol, *T. wilfordii* can be an alternative herbal treatment for cancer.

Methods:

- 95% ethanol extract from the roots of *T. wilfordii* at varying dosages
- *In vitro* study:
  - Measure proliferation of cell, cell vitality, cell survival/cell apoptosis, and cell cycle arrest. Perform cell toxicity assay.
- *In vivo* study:
  - Injected different cancer cell types into zebrafish and white mice.
  - Measure anti-angiogenic property in zebrafish embryos.
  - Observe indications of adverse effects in mice. Weekly blood tests and weighing for 8 weeks.
  - Sacrifice mice at the end of the study to examine internal organs.

Should the Experiment Fail:

- If fail in terms of efficacy (and safety), research should turn to natural products and combination drugs.
- If fails in term of safety alone, then research combinations of herbs that may have been used with *T. wilfordii*.

References

American Cancer Society. (n.d.) Cancer Facts & Figures 2015. Retrieved from http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/index

Centers for Disease Control and Prevention. (2013). Leading Causes of Death. Retrieved from http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm

He, M., Liu, L., Ge, M., Shaw, P., Jiang, R., Wu, L., & But, P. (2009). Antiangiogenic activity of *Tripterygium wilfordii* and its terpenoids. *Journal of Ethnopharmacology, 121*, 61-68. doi:10.1016/j.jep.2008.09.033

Liu, J., Jiang, Z., Liu, L., Zhang, Y., Zhang, S., Xiao, J.,…Zhang, L. (2010). Triptolide induces adverse effect on reproductive parameters of female Sprague-Dawley rats. *Drug and Chemical Toxicology, 34*(1), 1-7. doi:10.3109/01480541003774358

Kiviharju, T., Lecane, P., Sellers, R., & Peehl, D. (2002). Antiproliferative and proapoptotic activities of triptolide (PG490), a natural product entering clinical trials, on primary cultures of human prostatic epithelial cells. *Clinical Cancer Research, 8*, 2666-2674. Retrieved from http://clincancerres.aacrjournals.org/

Pang X., Yi, Z., Zhang, J., Lu, B., Sung, B., Qu, W.,…& Liu, M. (2010). Celastrol suppresses angiogenesis-mediated tumor growth through inhibition of AKTA/mammalian target of paramycin pathway. *Cancer Research, 70*(5), 1951-1559. doi:10.1158/0008-5472.CAN-09-3201

Peng, B., Xu, L., Cao, F., Wei, T., Yang, C., Uzan, G., & Zhang, D. (2010). HSP90 inhibitor, celastrol, arrest human monocytic leukemia cell at U937 at G0/G1 in thiol-containing agents in reversible way. *Molecular Cancer, 9*(79), 1-13. doi:10.1186/1476-4598-9-79

Piron, F., Ching, C., Peng, E., Ching, H. (2000). Consumers’ Perceptions of Chinese Vs. Western Medicine. *Advances in Consumer Research, 27*, 125-130. Retrieved from http://www.acrwebsite.org/volumes/8372/volumes/v27/NA-27

Yang, S., Chen, J., Guo, Z., Xu, X., Wang, L., Pei, X., … & Zhang, L. (2003). Triptolide inhibits the growth and metastasis of solid tumors. *Molecular Cancer Therapeutics, 2*, 65-72. Retrieved from http://mct.aacrjournals.org/

Acknowledgements

I would like to thank Professor Boyes and my TAs for helping me with the research and writing process, and Dr. Zhang from the Department of Medicinal Chemistry in the School of Pharmacy for helping me to design my proposed experiment.