Journal of Integrative Oncology
ISSN: 2329-6771

Smith, J Integr Oncol 2013, 2:2
DOI: 10.4172/2329-6771.1000e106

Editorial

What's in a Dose? Evaluating the Herbal and Nutritional Supplement Pre-Clinical Literature

Judith A Smith[1,2*]

[1]Division of Pharmacy and Department of Gynecologic Oncology & Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[2]Department of Gynecology, Obstetrics & Reproductive Sciences and Department of Pediatrics, UT Health- University of Texas Medical School, Houston, Texas, USA

As every investigator in integrative medicine, I am often asked does this supplement have activity in human, is it safe and for me often does it prevent/treat/cause cancer? While the peer reviewed literature in integrative medicine and in particular herbal and nutritional supplements has grown exponentially in the past two decades, the clarity of an answer is as clear as mud in many cases. In my opinion the crux of the issue is that there are limited guidelines in how to go about designing appropriate pre-clinical studies for herbal and nutritional studies. From a pharmacology perspective, one of the primary issues contributing to the inconsistency and conflicting data is how the "dose" for the study is selected.

To protect the innocent because I do not believe anyone intentionally tries to design a poor study, I am not going to provide specific examples rather speak in generalities and those of you conducting research relevant to the discussion hopefully will pick up on it and make changes to ultimately improve future studies. For an example I am going to talk about the popular class of phytoestrogens. A few years ago as we embarked on our research endeavor to identify a safe and effective phytoestrogen; my research team pulled all the current literature on all the 18 agents that have been described as a phytoestrogen which interestingly can be categorized into eleven different, unrelated plants. In Table 1 is a summary of finding demonstrating the inconsistency between the pre-clinical safety & efficacy data and what has been reported/observed in clinical safety and efficacy data. Very often, we found there was significant inconsistency within pre-clinical literature. For example, some literature states maca does estrogenic activity while another studies said it did not. As we looked closer at the two mouse studies with conflicting data, we found one study used a dose of 1 g/kg (equivalent to 70 g/day dose for average 70 kg adult) which concluded maca does have estrogenic activity conversely the other study used dose of 4.3 mg/kg (equivalent to 300 mg/day dose for average 70 kg adult) that concluded maca has no estrogenic activity on uterus. This is greater than a 200-fold difference in dose so it is not surprising that there were two completely different conclusions. After reviewing the literature on nutritional and herbal supplements for many years, one can conclude when it comes to nutritional and herbal supplements enough of anything can give you a response/effect (good or bad). The question then becomes, is the dose even clinically relevant? When reviewing the literature or perhaps reviewing for this journal, one has to stop and look at study design and determine if the dose is even clinically relevant.

Unfortunately to date, there is an enormous deficit in the pharmacokinetic information for most of the herbal and nutritional supplements commonly being used and/or pursued for clinical activity. In the absence of data, I have proposed a "worse-case scenario" method of estimating the concentration achieved in human to determine correlative dose for our pre-clinical studies. There are three assumptions for this estimate: first it assumes 100% bioavailability which honestly is very unlikely for most nutritional and herbal supplements but it is a place to start; second it assumes no metabolism interactions, i.e. "first pass effect"; lastly we assume total body volume for 70 g adult of seven liters, so not taking any gender or body composition factors into consideration. Back to maca example above, the commonly recommended dose for maca is 900 mg twice a day. Using this as an example we estimated the maximum achievable concentration would be 128.6 µg/mL which we have used in our *in vitro* studies. For animal studies, the equivalent dose calculates to be 32 mg/kg which is almost 10× higher than the low dose above and approximately 30× lower than the higher dose above. The data from our study has been submitted for publication so I will leave you with cliff-hanger to see what we concluded about the estrogenic activity of maca.

The intent behind any pre-clinical study is to hopefully gain more perspective or understanding of the activity in the clinical setting. The current pre-clinical literature for herbal and nutritional supplements is challenging to interpret and it takes high level of scrutiny to draw any conclusions. As human nature prevails, you can find literature to support or conflict just about any aspect you want to hear-it's safe and effective or it's not. In the age of technology, our consumers/patients have easy access to information, often only sharing limited components of the data. The call to action needed is to start designing better pre-clinical studies, with the translational/clinical endpoint always in mind. Second, when serving as the reviewer of studies being submitted for publication-be critical and ask the difficult question is this clinically relevant dosing? Finally, when guiding consumers/patients on safety and efficacy be sure to consider if the data being used to support either perspective, it's safe and effective or it's not, is based on studies that used clinically relevant dosing.

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***Corresponding author:** Judith A Smith, Department of Obstetrics, Gynecology & Reproductive Sciences, UT Health- University of Texas Medical School, 6431 Fannin Street, Houston, Texas 77030, USA, Tel: 713-500-6408,Fax: 713-500-5474; E-mail: Judith.Ann.Smith@uth.tmc.edu

Received October 17, 2013; **Accepted** October 23, 2013; **Published** October 29, 2013

Citation: Smith JA (2013) What's in a Dose? Evaluating the Herbal and Nutritional Supplement Pre-Clinical Literature. J Integr Oncol 2: e106. doi:10.4172/2329-6771.1000e106

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Family	Name	Pre-clinical Efficacy Data	Clinical Efficacy Data	Data supporting Safety	Data proposing unsafe
Anagraceae	Evening Primrose (Oenothera biennis L.)	NR	√	√	√
Apiaceae	Dong Quai (Angelica sinensis)	√	X	√	√
	Anise (Pimpinella anisum)	NR	√	√	√
	Fennel (Foeniculum vulgare)	NR	NR	√	√
Araliaceae	American Ginseng (Panax quinquefolius)	√	NR	√	√
	Korean Ginseng (Panax ginseng C. A. Meyer)	√	√	√	√
	Siberian Ginseng (Acanthopanax senticosus)	√	√	√	NR
Arecaceae	Saw Palmetteo (Serenoa repens)	NR	NR	√	√
Brassicaceae	Maca (Lepidium meyenii)	NR	NR	√	NR
Cannabinaceae	Hops (Humulus lupulus)	√	√	√	NR
Fabaceae	Alfalfa (Medicago sativa)	NR	NR	√	√
	Fenugreek (Trigonella foenum-graecum)	NR	NR	√	√
	Licorice (Glycyrrhiza glabra)	√	√	√	√
	Red Clover (Trifolium pratense)	√	√	√	√
Lamiaceae	Chasteberry (Vitex agnus castus)	√	√	√	√
Linaceae	Flaxseed (Linum usitatissimum)	NR	NR	√	NR
Ranunculaceae	Black Cohosh (Cimicifuga racemosa)	√	√	√	√
Rubiaceae	Cat's Claw (Uncaria tomentosa)	NR	NR	NR	√

NR=not reported √=reported/confirmed X=INEFFECTIVE

Table 1: Demonstrating the inconsistency between the pre-clinical safety & efficacy data [1-17].