Good Practice in Traditional Chinese Medicine Research in the Post-genomic Era

GP-TCM

223154

D5.11

Report on the problems carrying out investigations of CMH in animal models

Document description	
Name of document	Report on the problems carrying out investigations of CMH in animal models
Abstract	The main problems of CHM in animal models studies are identified and several recommendations are proposed.
Document identifier	D5.11
Document class	Deliverable
Version	1
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Date of creation	4th November 2011
Date of last modification	25th November 2011
Status	Final
Destination	European Commission
WP number	WP5

CURRENT PROBLEMS IN CARRYING OUT CHM STUDIES IN ANIMAL MODELS

We have analyzed the English publications reported in MedLine (ISI Web of Knowledge) regarding TCM and animal model studies, with the following aims: 1) To gain an overview of the general features of the studies on TCM and, particularly, of those studies involving animal models of disease (categorized according to conventional medicine). 2) To evaluate the present state of animal studies in relation with the need of scientific proof of the efficacy of CHM and the specific problems found in these studies.

Around 25% of TCM studies were done in animals (8952 references out of 29319 total references on TCM), these data being similar to those found for animal studies in the conventional medicine field of antineoplastic agents (54276 references in animals out of 236768 total references on antineoplastic agents). Most references of animal studies of TCM were published in 2000-2011 (5813 vs 3139 in 1950-1999), these data showing also a similar distribution to that found in the field of non-Chinese plant medicine studies in animals (6596 references in 2000-2011 vs 604 references in 1950-1999). Taking together, these data indicate that the animal studies in TCM and conventional medicine share the same features in the analyzed parameters.

The excellent review on scientific proof and clinical validation of CHM formulations (Yuan & Lin, 2000) states in its summary that it requires a rigorous approach that includes chemical standardization, biological assays, animal models, and clinical trials. The review specifically indicates that the effect of the CHM formulation should be tested on animal models for a particular health condition (Yuan & Lin, 2000). Accordingly, we have focused the present state of animal studies in relation with the need of scientific proof of the efficacy of CHM.

Another relevant issue is the type of formulations included in our study. CHM act multi-systemically and are often administered as a decoction, i.e., as a combination of multiple herbs in which the individual constituents may be difficult to determine. Therefore, in terms of addressing this challenge, researchers on the whole try to research into efficacy of either a single or small combination of a few active ingredients, which cannot fully recapitulate the effect of the complex mixture. This is why we have focused this part of our study on CHM preparations consisting of .herbal mixtures of 3 or more herbs prepared following the principles of TCM.

Regarding the animal models analyzed, most animal studies of CHM published in English deal with animal models which reproduce the diseases considered in conventional medicine and not with animal models of the human disease patterns considered in TCM (perhaps because the intrinsic problem of replicating in animal models the human disease patterns remains

unsolved). Therefore, our analysis of animal studies in CHM has been focused on animal models of diseases described in conventional medicine.

We have stated above the need of animal studies to give evidence-based proof of the efficacy of the CHM formulations. This need led us to identify the more usual problems of the animal studies of CHM in order to give recommendations for further studies. We chose cancer as a sample of the whole field of animal studies of CHM and the experimental design of papers in English written between 2000 and 2009 was analyzed. Most of the papers surveyed did not use randomization (72%) or blinding (98%) to reduce bias in animal selection and outcome assessment. Only 50% of studies used group sizes >5, 40-50% had appropriate statistical analyses and included a relevant control. There was general evidence of efficacy of the test CHMs in most reported papers-the level of which did vary but the CHMs reported were generally shown to be highly efficacious. However, variation in tumour size within experiments was not shown in 41% of studies but where shown was >10% in 34% studies. In addition there was very few cases where biomarkers of response linked to the mechanism of action of the test CHM were used. The clinical relevance of these studies was difficult to dissect out and compare to Western medicines since (i) the majority of studies were performed with treatment starting early in the study (39%), whereas only 19% of studies allowed tumours to become established before clinically-relevant treatment of established lesions was initiated. Furthermore, in a large portion of studies it was unclear when treatment was started (42%). (ii) only 20% studies compared test CHM effects with conventional medicine standard of care agents and (iii) there was little report of toxicity (where defined, it was associated to weight loss). In addition only 14% studies stated adherence to animal welfare guidelines and ethical committee compliance.

RECOMMENDATIONS

These issues suggest that the whole field of animal studies of CHM needs to be improved to ensure the subsequent utility and validity of the knowledge base that is used to inform future research in CHM. Worth to mentioning, most problems identified here are not specific of CHM, as shown by previous surveys of publications describing animal research and assessing specific aspects of experimental design, statistical analysis and reporting (see for instance Kilkenny et al, 2009). But, in view of the need of scientific proof of efficacy, we strongly recommend adherence to the recently published ARRIVE (Animal Research: Reporting *In Vivo* Experiments) guidelines (Kilkenny et al, 2010) for future animal studies of CHM. It is also interesting, the use of specific guidelines for particular diseases (i.e., Workman et al, 2010 for animal studies of cancer).

NETWORKING AND ACHIEVEMENTS:

Successful contribution of WP5 and WP4 members to this deliverable took place. Experts in animal models, in vitro models as well as cancer have revised bibliography regarding TCM in animal models and delivered reflexions in documents that have been considered as valuable material to build this deliverable and most importantly, the review “Animal studies of Chinese Herbal Medicine from the perspective of conventional medicine” already submitted to J Ethnopharmacology. On the other hand, several issues addressed in the preparation of this draft have been shared with WP4 and contribute to the review “Omics techniques in systems biology approaches to Traditional Chinese Medicine research: present and future” recently submitted to J Ethnopharmacology.

Deliverable 5.11 was originally planned in order to identify key problems in TCM and animal models studies. Through the extensive literature review made by WP5, quality control of the herb preparation, appropriated animal models for diseases as well as appropriated parameters to be analyzed in the models are the critical issues to be improved in those studies, as it was detailed in the review “Animal studies of Chinese Herbal Medicine from the perspective of conventional medicine” already submitted to J Ethnopharmacology

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