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Elaboration of a priority list of CMH for future research in CMH in animal models

Document description	
Name of document	Elaboration of a priority list of CMH for future research in CMH in animal models
Abstract	After reviewing the existing evidence in the literature of the value of CHM in animal models of cancer and fibrosis (as a sample of the whole field of CHM studies in animals), it is very difficult to generate a priority list because there are not enough good quality studies performed by independent research groups to support efficacy of CHM In animal models in cancer or fibrosis
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INFORM ON THE ELABORATION OF A PRIORITY LIST OF CHINESE HERBAL MEDICINES FOR FUTURE RESEARCH IN ANIMAL MODELS

In the GP-TCM technical annex, the priority list (D5.5) is found immediately after deliverable D5.4: Review of literature relating to Chinese Herbal Medicines (CHM) in animal model and elaboration, circulation and discussion of the corresponding report. Report of the agreed conclusions. The reason behind this order is that the review of the literature should give us the foundations for generating a priority list.

As stated in D5.4 volume II, in the WP5 kick-off meeting it was decided to undertake an in-depth review in cancer which was felt could be considered as a significant sample of the state-of-the-art in CHM studies in animals: according to MedLine, oncology is one of the most active medical areas in CHM in the last 10 years (see Report on Deliverable D5.4, Volume I). This is because cancer is one of the most common diseases but remains associated with poor prognosis and therefore an excellent target for CHM. There is a long history that traditional Chinese medicine (TCM) has been used to treat human malignant diseases due to its significant efficacy in a clinical setting, albeit in not such a regulated manner as in the West. Recently more and more scientists are getting interested in the role of Chinese medicine in cancer therapy, and therefore, a large number of experimental studies assessing the anti-cancer effects of TCM have been carried out.

It is essential to evaluate CHM efficacy and toxicity with animal models *in vivo*, but it is a tough challenge for CHM to establish suitable animal models for judging CHM efficacy and toxicity, because CHM are used as combinations and act multi-systemically. Furthermore in terms of addressing this challenge, researchers on the whole try to reaserch into efficacy of either a single or small combination of a few active ingredients from CHM in the research, which cannot fully recapitulate the effect of the complex mixture.
This is why we have focused our study in 'true' CHM preparations (i.e.Herbal Mixture of 3 or more Herbs prepared following the principles of TCM).

However, in our recent report communication to the Congress of the International Society of Ehtnopharmacology (Albacete, Spain, October 2010), we found that in the last 10 years there were only 6 published studies in Journals with an IF > 4 (this is our quality standard) involving 'true' CHM For comparison, for Western anti-neoplastic agents, there were in the last 10 years more than 3,200 citations having an IF >4. In a similar way, in an ongoing review on fibrotic diseases we have been unable to find any citation having an IF > 4. The same seems to be true for psoriasis and migraine. For the papers on cancer, if we lower the IF cut-off to 3, instead of 4, we recover only 7 papers written in English since 1950 in which true CHM was used (in the case of fibrosis the number is 0). That is to say: in cancer, with an IF set to 3 we get 1 paper more than when the IF was set in 4. In fibrosis, there are not papers recovered after lowering the IF from 4 to 3. So, it seems that lowering IF does not make a big difference, unless we lower the IF further. Another problem found in our analysis is the generalized use of non-standardized research materials (in terms of herbs and herbal preparations), which are likely to not support reproducibility and comparability of research on the same herbs and thus significantly reduce the scientific value and impact of these studies.

In the case of cancer, 665 papers (written in any language) devoted to studies in animals have been published since 1950 (the figure is 171 for papers on fibrosis during the same period). In our opinion, it is a very low number of studies along a 60-year period and, in fact, the number of studies involving true CHM is considerably lower. In the case of cancer, in which the vast majority of the papers written in English had only Chinese only 7 of the 35 papers with an IF > 3 (that is to say 20% of the papers) involved true CHM. If we extrapolate this ratio to the 665 papers, there must be around 500 papers in which true CHM is not used. Therefore, with such a limited number of animal studies involving true CHM it would seem that research of true CHM in animals has not been a priority for CHM studies. This is one of the reasons why we do not have enough material to scientifically support a priority list

It can be argued that an IF set at 3 is a very tight constraint that probably eliminates many good or reasonably good papers**.** However, the minimal standard of quality for studies in animals in Western Countries is the IF. We use the word 'minimal' because even the cancer studies of CHM with an IF > 3 had important methodological problems (to be published in our next report) regarding the source of the plants, the stability of the decoctions, the reproducibility of the studies using materials from other sources, etc. Even they have problems from the point of view of the absolute absence of diagnosis following the principles of TCM, comparison with Western standard drugs, etc (see our D5.4 II and D5.8 report and Xiaodong Cheng's manuscript on CHM in animal models in cancer) If we generate a priority list without including the IF as a minimal quality standard, then we will have generated a further review leaving CHM in its current 'neither-proven-nor disproven' medicinal status state. We think it is much better to recommend more studies in the area whose results will support the future generation of a priority list.

Therefore, it seems unlikely that we could find in other areas of disease a relevant number of papers with an IF > 4. It can be argued that we could generate priority lists using other criteria, such as the treatment of difficult diseases in the EU[1]. However, it is likely that there will be, at best, only one good reference per selected disease on the treatment with true CHM. How could we possibly recommend further research on the treatment of a particular disease based upon just one good reference?. Regarding the generation of priority lists based in either the most mature in vitro studies (to move onto animal work) or in CHM clinically proved, there are other WPs with better data than WP5. Perhaps it is the right moment to share these data with us.

In summary, these data suggest to focus our research not on complex CHM formula but on the medical herbs which have anti-tumor activities (again as a sample of the whole field of CHM studies in animals) and have the potential to be developed into new drugs for the clinical application.

[1] In fact, in our kick-off meeting, priority areas were preliminarily identified: cardiovascular diseases, cancer, pain, fibrotic diseases, CNS diseases and COPD-asthma (see D5. 1 report).

APPENDIX I: WP5 TCM PRIORITY LIST

	Chinese Pharmacopoeia species (CP05 English)	Accepted Latin scientific name (*Flora of China*) or other comment	Part used in TCM	Pharmaceutical name (from Chinese Pharmacopoeia 2005 (N.B. these names are reversed in the CP2010 e.g. 'Rhizoma Alismatis' becomes 'Alismatis Rhizoma')	Chinese name (pin yin)	Latin scientific synonyms 1: from *Flora of China* (http://flora.huh.harvard.edu/china); 2: additional synonyms from *World Checklist of Selected Plant Families* (http://apps.kew.org/wcsp)
	The following 5 species are those used in the TCM formula: "Zhu-Sha-An-Shen-Wan"					
1	*Rhizoma Coptidis or golden thread*	*Rhizoma Coptidis*	Rootback	Rhizoma Alismatis	Huang-Lian)	**Coptis chinensis Franch, Coptis deltoidea C.Y.Cheng et Hsiao, Coptis teeta Wall.**
2	*Cinnabar (HgS)*	*Cinnabar (HgS)*	Mineral powder	Cinnabar	'zhu-sha'	**Cinnabar (HgS)**
3	*Angelica Sinensis*	*Angelica Sinensis*	Rootback	Angelica Sinensis	'dang-gui'	**Angelica Sinensis**
4	*licorice root*	Glycyrrhizae Uralensis	Rootbark	licorice root	'gan-caoi'	**Glycyrrhizae Uralensis, or Licorice root**
5	*Rehmannia glutinosa* Libosch.	*Rehmannia glutinosa* (Gaertner) Liboschitz ex Fischer & C. A. Meyer	rhizome	Radix Rehmanniae Praeparata	'Di-Huang'	**Rehmannia glutinosa Libosch.**
	The following 4 species are those used in the TCM formula: "Huang-Dai-Pian"					
1	Realgar (As4S4)	*Realgar (As4S4)*	Mineral powder	Realgar	xiong-huang'	Realgar
2	NATURAL INDIGO	natural indigo indigo naturalis	Leaf. Whole plants	natural indigo indigo natur	qing-dai	Indigo Naturalis Rhizoma et Radix
3	Pseudostellaria heterophylla	Pseudostellaria heterophylla	Root	Pseudostellaria heterophy	'Tai-zhi-shen'	root of the false starwort
4	Salviae Miltiorrhizae	Salviae Miltiorrhizae	Root	Salviae Miltiorrhizae	'Dan-shen'	Salvia, Salviae Miltiorrhizae
	The following species had been requested at the meeting: There are concerns about cinnabar and realgar					
5	Cinnabar (HgS)	Cinnabar (HgS)	Mineral powder	Cinnabar	'zhu-sha'	
6	Realgar (As4S4)	Realgar (As4S4)	Mineral powder	Realgar	Xiong-huang'	

All the above species are frequently used in TCM and it is hoped that the different WPs can assist us to gather data on these species - especially