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

GP-TCM

223154

D5.4

Review of literature relating to CHM in animal model and elaboration, circulation and discussion of the corresponding report. Report of the agreed conclusions – Volume I

Document description	
Name of document	Review of literature relating to CHM in animal model and elaboration, circulation and discussion of the corresponding report. Report of the agreed conclusions - VOLUME I
Abstract	The report is focussed on WP5 central question A: What kind of research?
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1. SUMMARY

In the WP5 kick-off meeting it was decided to start with a preliminary review focused on the current status of CHM studies in animals. Among the central questions proposed (please see page 11), the present report is focussed in Central Question A: What kind of research? We first searched the PubMed (NIH) and the MedLine (ISI web of knowledge) database, using MeSH terms, to get results for our central question: What kind of research? We retrieved 6.328 references on animal studies of CHMs for the period 1950-2009. Most references (3.487; 55.10 %) were published from 2000-2009. The same intensification of activity in the past ten years was observed in research in CHMs (related or not to animal studies) and in non-Chinese plant medicine (56 %), but not in research in other traditional Chinese medicine practices such as acupuncture (41 %), or Western medicines such aspirin (31%). A very significant number of papers (46.92 % in Chinese; 4.27 % in other languages) are not readily accessible and readable for the international scientific community, making CHMs a 'forbidden' area for Western researchers. At least partially due to the handicapped access to relevant original literature, Western researchers generally do not lead research on CHMs, although they do participate as co-authors. In contrast, the activity of Chinese scientists in this particular area of research is overwhelmingly dominant and a vast majority (>95%) of the papers published in English, either in China or abroad, had authors with Chinese names. The most active areas of research on CHMs involving animal models were; Pharmacology & Pharmacy (359; 5.67 %), Biochemistry & Molecular Biology (291; 4.60%), Plants Sciences (184; 2.91%), Cell Biology (142; 2.25%), Genetics & Heredity (93; 1.47%) and Inmunology (91; 1.44%). We concluded fron this first part of the study that: (i) The past 10 years witnessed an specific surge of publications on phytotherapy, which includes CHM studies in animal models of disease; (ii) Chinese scientists play a major role in these studies, while involvement by international scientists as first or last authors has not significantly changed in the past 10 years; and (iii) language issue is still a major barrier for the international community to get access to CHM literature and to be more actively involved in this emerging area of research. In a second step, an in-depth review in cancer was undertaken. It will be taken as a significant sample of the state-of-the-art in CHM studies in animals. In the present report we show the preliminary results of this in-depth review. They were found only 665 references for the period 1950-2009. half of the references were published in Chinese journals without an impact factor (IF). and a great majority of journals with IF where these studies were more frequently published had IFs < 4. This is in sharp contrast to papers on antineoplastic agents in animals, >90%; (43.276) were written in English and 7 out of top 13 publishing journals had an IF greater than 4. However, for research in phytotherapy in animal models of cancer, only 2 out of top 13 publishing journals had an IF greater than 4. On the other hand, most CHM materials used for the treatment of animal models of cancer (crude herbs, dried herbs, powder, extracts, etc) were commercial, but data on authentication and quality control were generally missing. In particular, it is a very frequent practice of Chinese research teams to use herbs of unknown origin, which are subjected to a variety of extraction procedures to render extracts whose composition is unknown. The non-standardized research materials could poorly support reproducibility and comparability of research on the same herbs and thus significantly damp the scientific value and impact of these studies. It is concluded from this second part of the study that there are not many papers on cancer in animal studies of CHM and they are generally published in low IF journals, possibly due to the lower IF found in phytotherapy studies but also to less stringent authentication and quality control of CHM materials and the dubious reproducibility and reliability of CHM studies.

Perspectives: The group will continue working towards achieving their targets (i.e. unanswered WP5 central questions) in the next 12 months. Central Questions B and C will be addressed in the next report (October 31st, 2010) and the remaining Central Questions in the report after (April 30st, 2011). The deliverables D5.7 and D5.8, which are due on October 31st, 2010) will be delivered on time.

2 REPORT

2.1 Introduction

Former deliverables D5.4 to D5.6 (D5.4- Review of literature relating to CHM in animal models of disease and elaboration of a priority list for further research. Report on the reviewed literature relating to CHM in animal models of disease, D5.5- Circulation and discussion of the report, D5.6- Report on agreed conclusions of the review of literature) have been merged into a single deliverable titled: *Review of literature relating to CHM in animal model and elaboration, circulation and discussion of the corresponding report. Report of the agreed conclusions*. Annex I shows the labour division in WP5 for this deliverable. In the WP5 kick-off meeting it was decided to start with a preliminary review focused on the current status of CHM studies in animals. We addressed first the central question "What kind of research?"[1] Next, taking into account that most WP5 members and experts have experience in cancer research, an in-depth review in cancer was undertaken. It will be taken as a significant sample of the state-of-the-art in CHM studies in animals.

2.2. Report on central question A: What kind of research?

2.2.1 Statistics on the research on herbal preparations in TCM

Database: Pubmed (NIH), MedLine (ISI web of knowledge) and Journal of Citation Report (ISI web of knowledge). The search was done using MesH terms (MeSH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts).

Periods analyzed: 1950-1999 vs 2000-2009

MesH: Drugs, Chinese Herbal Medicine OR Medicine, Chinese Tradicional (terms included: Chinese Medicine, Traditional; Chinese Traditional Medicine; Chung I Hsueh; Hsueh, Chung I; Medicine, Chinese Traditional; Traditional Chinese Medicine; Traditional Medicine, Chinese; Zhong Yi Xue).

References found: 23,915 (18,113 for Drugs, Chinese Herbal Medicine and 7,830 for Medicine, Chinese Traditional)

Controls: In order to assess the scientific production in the field of herbal preparations in Traditional Chinese Medicine, we analyzed several related fields of research:

Acupuncture: control of another TCM field
Homeopathy: control of another alternative medicine
Statins (C10AA): the lead compound, mevastatine, was found in Penicillium citrillum[2].
Aspirin: control as a western drug.

Table I. Search strategy.

SEARCH	DESCRIPTION
MTC GENERAL	"Drugs, Chinese Herbal)" [MeSH] OR "Medicine, Chinese Traditional" [MeSH]
ASPIRIN	"Aspirin"[Mesh]
HOMEOPATHY	"Homeopathyl"[Mesh]
STATINS	"Hydroxymethylglutaryl-CoA Reductase Inhibitors "[MeSH] NOT "red yeast rice "[Substance Name] NOT "Meglutol"[Substance Name] NOT "Chinese"[Language]
ACUPUNCTURE	"Acupuncture"[Mesh] OR "Acupuncture Therapy"[Mesh]

[1] See Annexes.

[2] "red yeast rice" was excluded since is used in TCM. "Meglutol" was also excluded since it belongs to another pharmacologic Group (C10AX).

Period 1950-1999 vs period 2000-2009

The number of references for Drugs, Chinese Herbal OR Medicine, Chinese Traditional in 2000-2009 is around 30% higher than that found for the period 1959-1999 (Table II). This recent intensification in the research in the field seems to be specific for Chinese herbal preparations, since the acupuncture control exhibited the opposite behaviour (Table II). In fact, there is also an increasing interest in the research in medicinal plants in the rest of the world (results are not shown), which is not found in other alternative medicines such as homeopathy (Table II) nor in Western conventional drugs as aspirine (Table II).

Table II. References for Drugs, Chinese Herbal OR Medicine, Chinese Traditional

	1950-1999		2000-2009		TOTAL
CHM in context	ARTICLES	%	ARTICLES	%	
CHM	10,369	43.36	13,546	56.64	23,915
ACUPUNCTURE	7,404	58.99	5,146	41.01	12,550
HOMEOPATHY	2,025	58.39	1,443	41.6	3,468
ASPIRIN	22,187	69.11	9,919	30.89	32,106
STATINS	2,067	15.66	11,135	84.44	12,049

	ENGLISH		CHINESE		OTHERS	
CHM in context	ARTICLES	%	ARTICLES	%	ARTICLES	%
CHM	10,877	45.48	11,328	47.37	1710	7.15
ACUPUNCTURE	7,781	62.01	2,133	16.99	2,636	21.00
HOMEOPATHY	2,363	68.14	0	0	1,105	31.86
ASPIRIN	26,368	82.13	152	0.47	5,586	17.40
STATINS	12,049	91.27	29	0.22	1,124	8.51

Language of publication and authors

Less than 50% of the published work on Drugs, Chinese Herbal OR Medicine, Chinese Traditional is written in English (45.69% is the figure), which is a worrying finding since any important research work published in Chinese is not available for the rest of the world. This is a very specific feature of Chinese herbal medicine since it is not found in any control. It is particularly striking the difference with aspirin (Table IId), where references in Chinese are less than 0.5%

We have to say that the rest of the world, in turn, pays little attention to Chinese herbal medicine, since the vast majority (>95%) of the authors of the English references –published in China or abroad- have Chinese names (results not shown).

The results on the language of publication and authorship indicate that there is a long way ahead until the research in Chinese herbal medicine achieves the same degree of internationalization than drug research.

Most active areas

The statistics retrieved from the ISI Web of Knowledge indicated that the most active areas in Chinese herbal medicine were the following (number of references is indicated into brackets): integrative & complementary medicine (4,108); immunology (3,978); cardiovascular system & cardiology (3,442); haematology (3,325); gastroenterology & hepatology (3,267); neurosciences & neurology (2,523); oncology (2,396)

2.2.2 Statistics on the research of herbal preparations in TCM in animals

Our search strategy was ((("Animals, Laboratory"[Mesh] OR "Disease Models, Animal"[Mesh] OR "Dogs"[Mesh] OR "Cats"[Mesh] OR "Rodentia"[Mesh]) NOT "Cells, Cultured"[Mesh]. Interestingly, the research in animals is around 25% of the work in the field of Chinese herbal medicine (6,328 references out of 23,915 total references). These results are similar to those found for antineoplastic agents (see below), which highlights the fact that animals are so relevant to TCM research than they are to conventional medicine.

Further analysis of the references (Table III) indicated that research in animals exhibit the same behavior found for the whole field of Chinese herbal medicine (compare to Table IIa).

Table III. Research in herbal preparations of Traditional Chinese Medicine in animals

	1950-1999	2000-2009	TOTAL
ENGLISH	1209	1880	3089
CHINESE	1572	1397	2969
OTHERS	60	210	270
TOTAL	2841	3487	6328

Statistics on plant medicine (excluding CHM) in animals

The results shown above are not very promising. However, Chinese herbal medicine is more about plants and herbal extracts than about single active compounds (the grounds of antineoplastic agents). Therefore, we decided to analyze the published work on plant medicine. The search strategy excluded the Mesh terms for Chinese herbal medicine as well as the published work in Chinese to ensure that we mainly recovered the references on plant medicine not involving Traditional Chinese Medicine. We used the following search strategy: ((("Plants, Medicinal"[Mesh] OR "Plant Extracts"[Mesh]) OR "Phytotherapy"[Mesh]) NOT ("Drugs, Chinese Herbal"[Mesh] OR "Medicine, Chinese Traditional"[Mesh])) NOT Chinese[lang] AND ("Animals, Laboratory"[Mesh] OR "Disease Models, Animal"[Mesh] OR "Animal Experimentation"[Mesh] OR "Dogs"[Mesh] OR "Cats"[Mesh] OR "Rodentia"[Mesh]).

We found *22,743* references (20,732 in English) from which *12,746* were published in the last 10 years

. Table IV. Plant medicine studies in animals: journals more frequently used in the last 10 years

SOURCE	ARTICLES	%	IMPACT FACTOR (2008)
J ETHNOPHARMACOL	1703	13.30	2.260
PHYTOTHER RES	923	7.21	1.772
PLANTA MED	606	4.73	1.960
PHYTOMEDICINE	493	3.85	2.330
BIOL PHARM BULL	372	2.91	1.765
FITOTERAPIA	340	2.66	1.200
FOOD CHEM TOXICOL	270	2.11	2.321
INDIAN J EXP BIOL	257	2.01	0.599
J NAT PROD	221	1.73	2.843
J PHARM PHARMACOL	208	1.62	1.847
J MED CHEM	199	1.55	4.898
J AGRIC FOOD CHEM	192	1.50	2.562
LIFE SCI	174	1.36	2.583

The table indicates than more than 45% of the references are found in journals whose impact factor is lower than 3 (with the only exception of J Med Chem).

2.2.3 Animal studies of Chinese herbal medicines in cancer

We first analyzed the statistics of the MesH term Antineoplastic agents as a control to compare the data on Chinese herbal medicine:

Table V. Research in antineoplastic agents (non involving CHM)

SEARCH STRATEGY	REFERENCES (1950-present)	LAST 10 YEARS	ENGLISH
"Antineoplastic agents" [Mesh].	205,161	114,556	176,039
"Antineoplastic agents" [Mesh].NOT ("Drugs, Chinese Herbal)" [MeSH] OR "Medicine, Chinese Traditional" [MeSH])	203,789	113,606	175,178
"Antineoplastic agents" [Mesh] AND (("Animals, Laboratory"[Mesh] OR "Disease Models, Animal"[Mesh] OR "Dogs"[Mesh] OR "Cats"[Mesh] OR "Rodentia"[Mesh])	48,043	22,826	43,276

Our results indicated that i) most research in antineoplastic agents is published in English, ii) the "antineoplastic agents term" mainly includes non-TCM studies and iii) research in animals is around 20%: the same proportion than research in animals in TCM

We next analyzed the impact factor of the journals in which the work on antineoplastic agents in animals is more frequently published during the last ten years.

Table VI. Research in antineoplastic agents in animals: journals more frequently used in the last 10 years

SOURCE	ARTICLES	%	IMPACT FACTOR (2008)
CANCER RES	961	4.08	7.514
CLIN CANCER RES	823	3.50	6.498
J MED CHEM	497	2.11	4.898
MOL CANCER THER	437	1.86	5,003
ANTICANCER RES	417	1.77	1.390
INT J CANCER	391	1.66	4.734
CANCER CHEMOTHER PHARMACOL	362	1.54	2.740
CANCER LETT	335	1.42	3.504
BIOORG MED CHEM LETT	257	1.09	2.531
J BIOL CHEM	256	1.09	5.520
BIOORG MED CHEM	255	1.08	3.075
CARCINOGENESIS	235	1.00	4.930
ANTICANCER DRUGS	214	0.91	2.358

The published work (around 23% of the total published work) is found in journals whose impact factor ranges from 7.514 to 1.390 (Table VI). 7 out of 13 journals have an impact factor higher than 4.

We next analyzed the same parameters for animal studies of Chinese herbal medicine in the field of cancer. Our search strategy was (("Animals, Laboratory"[Mesh] OR "Disease Models, Animal"[Mesh] OR "Animal Experimentation"[Mesh] OR "Dogs"[Mesh] OR

"Cats"[Mesh] OR "Rodentia"[Mesh])]) AND (“Drugs, Chinese Herbal”"[Mesh] OR “Medicine Chinese Tradicional”"[Mesh]).

We found that half of the references are published in English and the other half in Chinese (Table VII), which again makes 50% of the research in the field unavailable for the rest of the world. Worth to mentioning it, during the last ten years there is a tendency to increase the publications in English.

Table VII. Cancer research in Chinese herbal medicine in animals

	1950-1999	2000-2009	TOTAL
ENGLISH	139	233	372
CHINESE	115	148	263
OTHERS	23	7	30
TOTAL	277	388	665

	1950-1999	2000-2009	TOTAL
ENGLISH	20.90%	35.04%	55.94%
CHINESE	17.29%	22.26%	39.55%
OTHERS	3.46%	1.05%	4.51%
TOTAL	41.65%	58.35%	100.00%

Table VIII. Cancer research in Chinese herbal medicine in animals: journals more frequently used in the last 10 years

SOURCE	ARTICLES	%	IMPACT FACTOR (2008)
ZHONGGUO ZHONG YAO ZA ZHI	40	10.36	------
ZHONG XI YI JIE HE XUE BAO	28	7.25	------
ZHONG YAO CAI	24	6.22	------
WORLD J GASTROENTEROL	23	5.96	2.031
ZHONGGUO ZHONG XI YI JIE HE ZA ZHI	23	5.96	------
J NAT PROD	16	4.15	2.843
AM J CHIN MED	10	2.59	1,058
BIOL PHARM BULL	9	2.33	1.765
CANCER LETT	9	2.33	3.504
J ETHNOPHARMACOL	7	1.81	2.260
J TRADITIONAL CHIN MED	7	1.81	------
LIFE SCI	7	1.81	2.583
ONCOL REP	7	1.81	1.524
CARCINOGENESIS	5	1.30	4.930
ACTA PHARMACOL SIN	4	1.04	1.676
INT J CANCER	4	1.04	4.734

Regarding the published work, we analyzed the journals more frequently used in the last 10 years until 0.5% of frequency (for clarity Table VIII summarizes the results found until 1%). They were 223 articles from which 115 (51.57%) had no impact factor (4 out of the 5 first journals). The impact factor ranges from 4.930 to 1.524 and only 2 out of 16 journals have an impact factor higher than 4 (Table VIII). Furthermore, only 9 references are published in

journals with an impact factor higher than 4, whereas the figure is higher than 3.200 for the published work in antineoplastic agents (Table VI).

The results shown above are not very promising. However, Chinese herbal medicine is more about plants and herbal extracts than about single active compounds (the grounds of antineoplastic agents). Although more than 51% of the total analyzed work on studies of Chinese herbal medicine in cancer is found in journals without impact factor, there is around 23% papers whose impact factor is similar to that found for plant medicine studies in animals. As we have previously shown, more than 45% of the references in the field of animal studies of phytotherapy are found in journals whose impact factor is lower than 3. And, specifically in the case of cancer, only 2 out of top 13 publishing journals had an IF greater than 4.

Most active areas in animal studies of Chinese herbal medicine in cancer

Finally, the statistics retrieved from the ISI Web of Knowledge indicated that the most active areas in animal studies of Chinese herbal medicine in cancer in the last 10 years were the following: (number of references is indicated into brackets): gastroenterology & hepatology (150); immunology (103); haematology (80); integrative & complementary medicine (63); respiratory system (39); toxicology (36); urology & nephrology (30); endocrinology & metabolism (22); obstetrics & gynecology (22); neurosciences & neurology (20);

2.3 Annexes

2.3.1. Labour Division

English papers

1. Identification of papers and circulation of PDFs: Laura Garcia & Gemma Olmos
2. Central Question A. What kind of research (type of paper, subject, type of CHM preparation, etc)? Javier de Lucio.
3. Central Question B. What was the quality of the research from the perspective of modern medicine? Sue Watson.
4. Central Question C. What was the quality of the research from the perspective of Traditional Chinese Medicine? Ye Zuguang (and Guangping Zhang) & Xiaodong Cheng
5. Central Question D. What was the efficacy and mechanism of action of the treatment? William Jia & Gemma Olmos
6. Central Question: Disease-specific central questions: Rajendra Kumari & De-An Guo & Liping Zhao (GI tract)
7. Central Questions on Toxicology Pierre Duez and Joelle Nortier
8. Recommendations on the application of functional genomics: Laura Garcia and Liping Zhao

Chinese papers

1. Identification of papers and circulation of PDFs: Ping Li
2. Central Question A. What kind of research (type of paper, subject, type of CHM preparation, etc)? Ping Li
3. Central Question B. What was the quality of the research from the perspective of modern medicine? De-An Guo & Sue Watson
4. Central Question C. What was the quality of the research from the perspective of Traditional Chinese Medicine? Ye Zuguang (and Guanping Zhang) & Xiaodong Cheng
5. Central Question D. What was the efficacy and mechanism of action of the treatment? Xuebin Dong
6. Central Question: Disease-specific central questions: De-An Guo & Rajendra Kumari & Liping Zhao (GI tract)
7. Central Question: Disease-specific central questions: Rajendra Kumari & De-An Guo & Liping Zhao (GI tract)
8. Central Questions on Toxicology Ye Zuguang

9. Recommendations on the application of functional genomics: Laura Garcia and Liping Zhao

Expected progress (time table)

a) Assignation (and acceptation) of duties. Ready by Early November
b) Identification of papers and circulation of PDFs. Ready by 20th November
c) Reports on central Questions: Ready by 12th November
d) Reports on Central Questions. Circulation of the assembled reports. Ready by 15th December
e) Discussion of the report. Conclusions by 30th December
f) Elaboration of a priority list. Ready by 15th January
g) Recommendations on the application of functional genomics. Ready by 30th January
h) Recommendations on best practice. Ready by 15th February
i) Report on the problems carrying out investigations on CHM in cancer. Ready by 1st March

Real progress

Only the identification and circulation of papers and the work on central question A have been finished. Some work has also been done on Chinese papers.

2.3.2 Central questions

The proposed central questions were

General (although several questions have been proposed in the context of cancer -the second step of our work- they apply to any disease, NOT only cancer.

A. What kind of research (type of paper, subject, type of CHM preparation, etc)?

a) Distribution of peer reviewed papers
b) Distribution of in vivo studies vs. animal models
c) distribution of non-clinical vs. clinical studies
d) distribution of purified compounds from TCM vs. extracts of TCM
e) distribution of chemical analysis vs. pharmacology vs.toxicology vs.PK…
f) distribution of studies involving functional genomics or other molecular biology analysis vs. non-functional genomics
g) reviews vs. experimental studies
h) Chinese vs. English, Chinese with English abstract vs. Chinese only
i) Evaluation of techniques involved in the research, especially functional genomics methods by broad definition.
j) difficulties that are unique for TCM animal studies
k) suggestions for improvement

B. What was the quality of the research from the perspective of modern medicine?

a) Which pathways are studied in tumor after CHM treatment
b) Biomarkers of response identified
c) Evidence of toxicity-weight loss, clinical signs
d) Was the agent compared to a Western standard of care (chemo/radiotherapy)?
e) Experimental design-numbers per group/variation in tumour size, relevant controls/appropriate statistical analysis
f) Evidence of compliance with relevant animal experimentation Regulatory Authorities-Home Office in UK for e.g.
g) Treatment regime, (starting treatment with the tumor implantation or after the tumor has been established)
h) With or without combination with conventional chemotherapy/radiotherapy

C. What was the quality of the research from the perspective of Traditional Chinese Medicine?

a) Would the animal model used in the study be approved by TCM doctors?
b) What signs and symptoms need to be assessed by a TCM doctor in experimental animal models of cancer. This will apply for the evaluation of tumor evolution after CHM treatment.
c) Is there an agreement in tumor diagnosis between western medicine and TCM?
d) Would the herbal treatment be approved by TCM doctors (particularly if there is not concomitant use of acupuncture or more herbs)?

D. What was the efficacy and mechanism of action of the treatment?

a) Tumor weight, size, mortality, survival time, metastasis
b) CHM as a preventive treatment
c) CHM as co-adjuvant treatments for secondary effects of conventional chemo/radiotherapy
d) Comparison between CHM cellular and molecular mechanism of action in tumor and conventional chemotherapy: there is a crosstalk?
e) Effect of CHM vs western chemotherapy in tumor microenvironment as well as immune system.

E. Disease-specific

a) What cancer types?
b) Cell lines versus patient's tissue?
c) What species and strains-zebrafish/rodents-nude/SCID/Nod-SCID mice?
d) Syngeneic versus xenogeneic systems
e) How complex are the models-sc versus orthotopic-maybe grade them?
f) Treatment of early lesion versus established/metastatic lesion?
g) Clinical relevance of administration route, dosage level, frequency?
h) Which types of cancers (based on organ origins) are most studied or most responsive to CHM treatment

F. Central questions to be taken into account (they need to be answered after the review)

a) Based on the findings of the review, what is controversial? What additional review is needed? Any areas of special importance? Why?
b) Is cancer (or some subareas of cancer) mature in CHM research and therefore can be proposed for further studies?
c) Which CHMs have the most convincing efficacy in animal models? Why?
d) What's the suggested future of these CHMs?
e) What good practice should be followed in animal studies of CHMs in cancer?
f) What are the current problems in carrying out CMH studies in animal models of cancer?
g) What future priority areas are recommended in animal studies of CHM in cancer? Why?

2.3.3 Preliminary work on 10 Chinese papers on CHM in animal models of cancer

General:

1. All papers are about the research of tumor treatment with TCM extract. TCM compounds. Although in these papers there are some certain effect of anti-tumor for TCM, but they are not drugs commonly used and widely approved by TCM doctors.

2. Study drugs in these papers are all TCM extractor compounds. The composition is complicated and we do not know the effective ingredients and the mechanism of tumor treatment , it causes the difficulty of repeating these experiments.

3. TCM (extract of single herb medicine or compound) has complicated component and extensive role. Many TCM can have some certain effect on tumor treatment through restraining links of tumor occurrence and development, as well as herb medicines in your papers have these effects. But for traditional Chinese medical science, they are not drugs for tumor treatment and rarely alone used for tumor treatment.

Central Question D. What was the efficacy and mechanism of action of the treatment?
Efficacy:

Paper ≠

1. Studies include report on recurrence, metastasis, and life span of mice transplanted with carcinoma cells. These involve mixed-component Recipe, as well as individual herb medicine.
2. Suppression of tumour growth, in xenografts in nude mice.
3. Suppression of proliferation of cancer cells in immunocompetent mice.
4. Anti-tumour and immune-modulating effect (of Scutellaria barbata extract in mice bearing hepatocarcinoma H22 cells-derived tumour).
5. Anti-cancer effect of various fractions extracted from (Dioscorea bulbifera) on mice bearing HepA.
6. (Pingfei Mixture's) two-way adjustment to cell proliferation in mice with tumour (inhibit tumour cell proliferation while promote T cell proliferation at the same time).
7. Effect on dynamic change in angiogenesis within the tumour tissue.
8. Augmentation of interventional therapy in non-resectable tumour [The application of Bletilla striata in the interventional therapy of hepatocellular carcinoma : a comparative study using ACI rat.]
9. Leukocyte increasing effect (of Shuanghuang Shengbai Granule) in tumour patients treated by chemotherapy, and its function on bone marrow hematopoietic microenvironment in mice.
10. Toxicity Attenuation and Efficacy Potentiation Effects (of Sijunzi Decoction on Bladder Carcinoma Treated by Chemotherapy in Mice)
11. Anti-oxidative capacity (of Acetoacetate and n-butanol extractive from C orbiculatus)
12. Promote general health, improve life quality.

Mechanism:

Paper ≠

1. Effect of Chinese medicine compound on angiogenesis in transplanted tumour of mice (through inhibition of VEGF, KDR/FLK-1 expression).
2. Inducing apoptosis and related gene expression in cancer cells grafted onto nude mice. mixed-component Recipe or single herb (*Sarcandra glabra*) extract.
3. Effect (of Astragulus injection) in enhancing anti-tumour metastasis action of dendrite cells.
4. Direct cytotoxic effect

5. Effects (of Yifei Kangliu Oral Liquid) on cell cycle and protein-nucleic acid synthesis of experimental lung cancer.
6. Effect (of Coptis Chinensis compound) on the gene expression in transplanted tumour tissue by cDNA microarray. To study the effect of up-regulation and/or down-regulation of genes.
7.Altered telomerase activity
8.Effect (of hydroxyl safflor yellow A) on blood vessel and mRNA expression with VEGF and bFGF of transplantation tumour in nude mice
9. Effect (of FuFang TengLiGen Mixture) on gap junction intercellular communication , GJI. Up-regulate the expression of connexion 43.
10. Suppression of carcinogenic gene: Preventive and therapeutic effects of qiongyugao on hepatocegular carcinoma via inhibition of the expression of HBxAg in hepatic carcinoma cells.
11. Enhance the expression of PTEN in liver: [Study of Antitumous Effect of the Complex Prescription of Chinese Crude Dru g in Athymic M ice with HCC]
12. Inhibit tumour growth via modulating endocrine effects [Lithospermum extract can inhibit the growth of MCF-7 cell and inhibit the level of estrogen and progestogen in mice.]
13. Inhibit tumour growth through modulating cytokine activities. [The Mechanism of Resveratrol on Anti-hepatoma Bel-7402 and Modulating IL-8 in Tumour model M ice]

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D5.4

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INTRODUCTION

In the WP5 kick-off meeting it was decided to start with a preliminary review focused on the current status of Chinese herbal Medicine (CHM) studies in animals. In a second step, it was decided that an in-depth review in cancer should be undertaken and would 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). And this is because cancer is one of the common diseases but remains associated with poor prognosis. There is a long history that traditional Chinese medicine (TCM) has been used to treat human malignant diseases due to its significant efficacy in clinic. 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-tumor effects of TCM have been carried out.

TCMs are popularly used by cancer patients, particularly those of East Asian ethnicity and/or those in the palliative phases of advanced disease. Various strategies have evolved for the treatment of tumors with TCM: i) Reducing pain, inflammation, swelling and tumor mass ii) Improving host resistance through preserving immune competence and enhancing the function of internal organs to counter chemotherapy-induced immune or myelosupression iii) Potentiating the effects of conventional radiation and chemotherapies iv) Preventing, controlling and treating the adverse effects of conventional treatment, including fatigue, weakness, gastrointestinal distress, loss of apetite, nausea, emesis and leucopenia.

Since TCM herbs are often administered as a decoction, i.e., as a combination of multiple herbs in which the individual constituents and their levels may be difficult to determine, their 'neither-proven-nor disproven' medicinal status is likely to prove durable. The evidence found in animal studies of CHM might help to reveal the clinical utility of TCM in cancer. Based on the literature in the past ten years, we reviewed the status of animal models using TCM for cancer research.

REPORT ON CENTRAL QUESTION B: What was the quality of the research from the perspective of modern medicine?

1. METHOD

A total of 192 research papers from 2000-2009 were reviewed. Of these 81% were English and 19% in Chinese with English abstracts. The papers in English papers were challenged with the following questions and % graphed as shown in the results section. Based on the answers to these questions an overall score was given to the paper between 1 (low) to 5 (high). The Chinese abstracts were also challenged where possible with the same questions, however insufficient data was available in English to fully evaluate these papers and therefore have been excluded from the analysis.

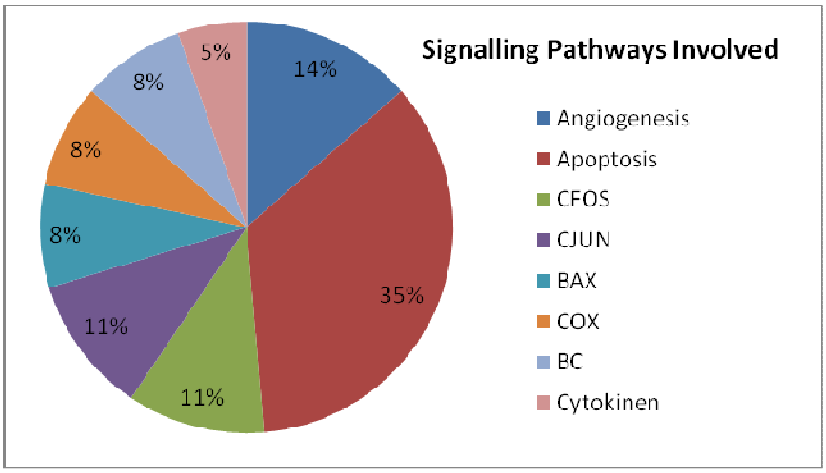
Table 1: Summary of questions

Question	Proposed answer format
Which pathways are studied in tumor after CHM treatment	Pathway stated
Biomarkers of response identified	Biomarker stated
Evidence of toxicity-weight loss, clinical igns	Yes/No with details
Was the agent compared to a Western standard of care (chemo/radiotherapy)?	Yes/No with standard of care stated
Experimental design: numbers per group variation in tumour size relevant controls appropriate statistical analysis	 <5, 5-10, >10 <10%, 10-20%, >20% Yes/No Yes/No
Evidence of compliance with relevant animal experimentation Regulatory Authorities- Home Office in UK for e.g.	Yes/No
Treatment regime, (starting treatment with the tumor implantation or after the tumor has been established)	Early/Established
With or without combination with conventional chemotherapy/radiotherapy	Yes/No with standard of care stated
Overall score	1 (low) to 5 (high)

2. RESULTS

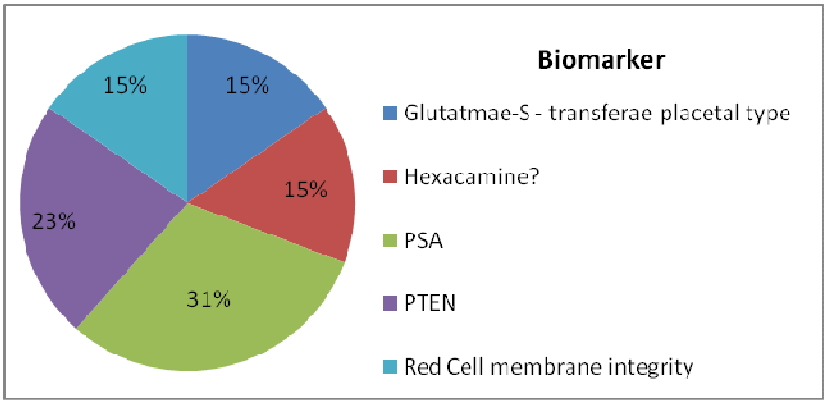
2.1 Which pathways are studied in the tumor after CHM treatment

Approximately 40% of the papers investigated cellular signaling pathways when evaluating the CHM. The most studied pathways were apoptosis (35%) and angiogenesis (14%).



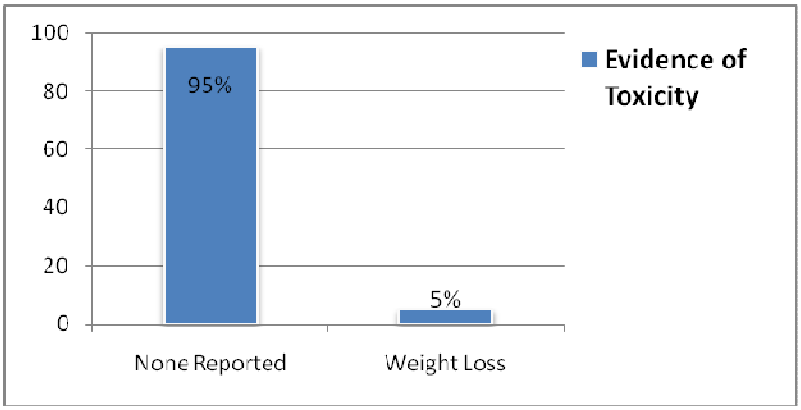
2.2 Biomarkers of response identified

Only 7% of the papers reported any biomarker of response when evaluating the CHM. The biomarkers included clinically relevant biomarkers such as PSA (31%).



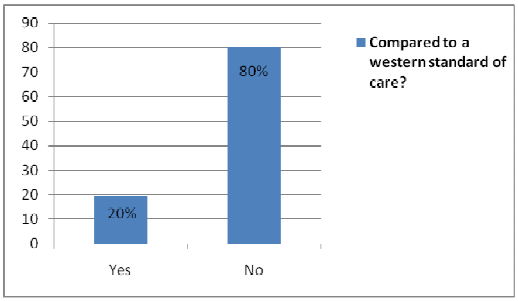
2.3 Evidence of toxicity-weight loss, clinical signs

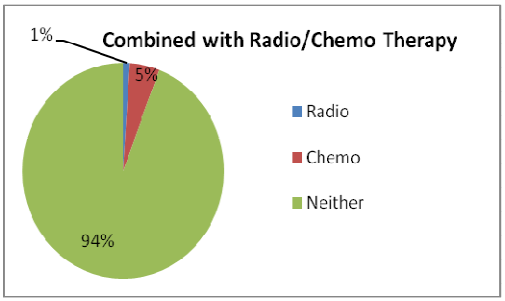
Approximately 5% of the studies reported any adverse effects, however a large majority did not assess this*.*



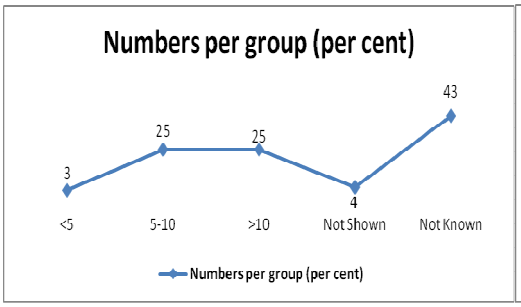
2.4 Was the agent compared to a Western standard of care (chemo/radiotherapy)?

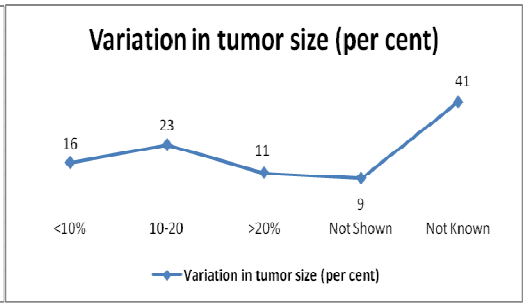
The majority of studies (80%) did not include a standard of care to compare alongside the CHM. Of the studies that did include a standard of care, chemotherapy was the preferred agent.Only a few studies (6%) investigated the combination potential with western standards of care.

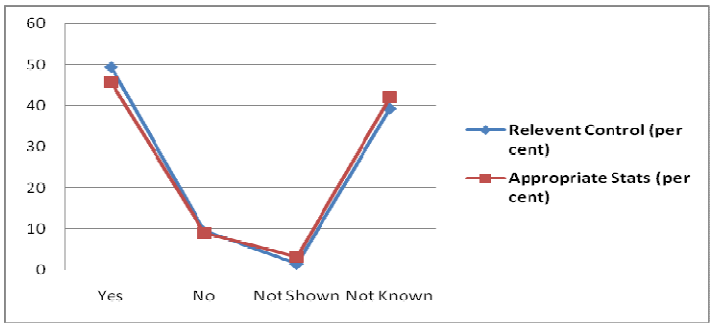




2.5 Experimental design-numbers per group/variation in tumour size, relevant controls/appropriate statistical analysis

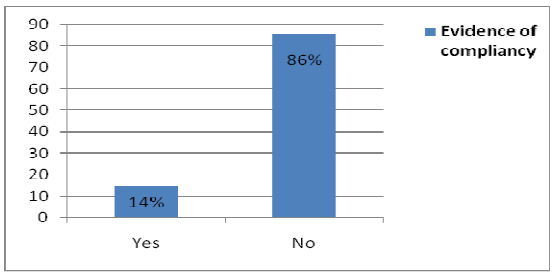






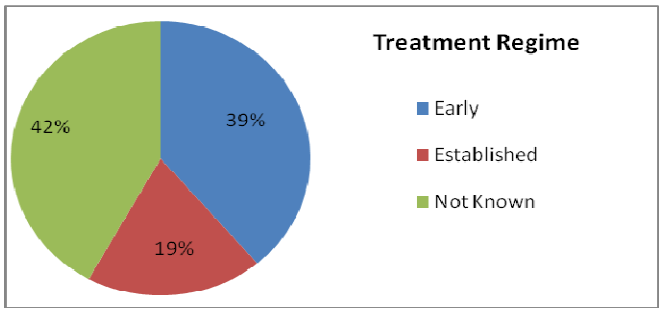
2.6 Evidence of compliance with relevant animal experimentation Regulatory Authorities-Home Office in UK for e.g.

Only 15% of the studies reported compliance with relevant regulatory authority for the use of animals in research.



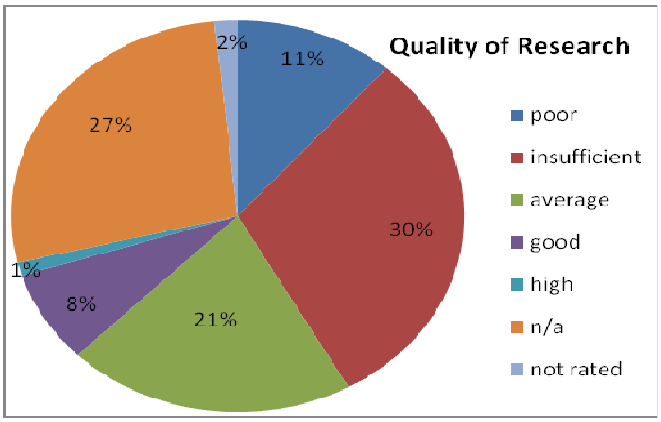
2.7 Treatment regime, (starting treatment with the tumor implantation or after the tumor has been established)

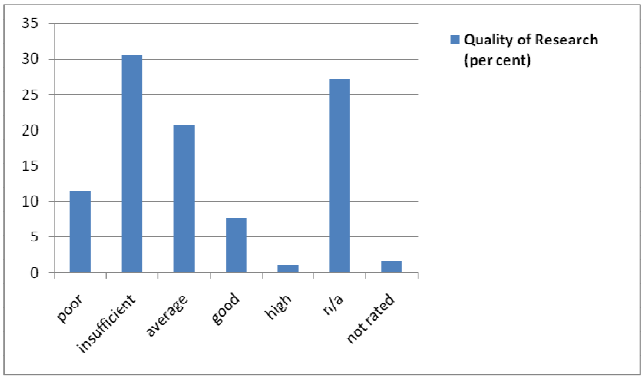
The majority of studies were performed with treatment starting early in the study (39%), whereas only 19% of studies allowed tumours to become established before treatment was initiated. Unfortunately in a large portion of studies it was unclear when treatment was started (42%).



Criteria for overall score

The majority of papers reviewed scored an overall mark of either 2 (30%) or 3 (21%). Only 1% of the papers were of excellent quality (score of 5). However 27% were Chinese papers which were not scored???





REPORT ON CENTRAL QUESTIONS: Disease specific questions

2. METHOD

A total of 192 research papers from 2000-2009 were reviewed. Of these 80% were presented in English and 20% in Chinese with English abstracts. The papers in English papers were challenged with the following questions and % graphed as shown in the results section. The Chinese abstracts were also challenged where possible with the same questions, however insufficient data in English was available to fully evaluate these papers and therefore have been excluded from the analysis.

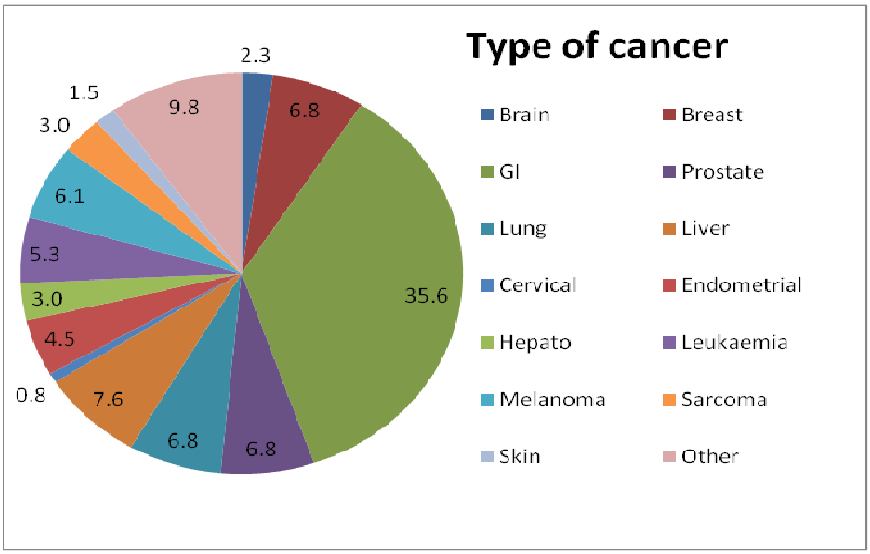
Table 1: Summary of questions

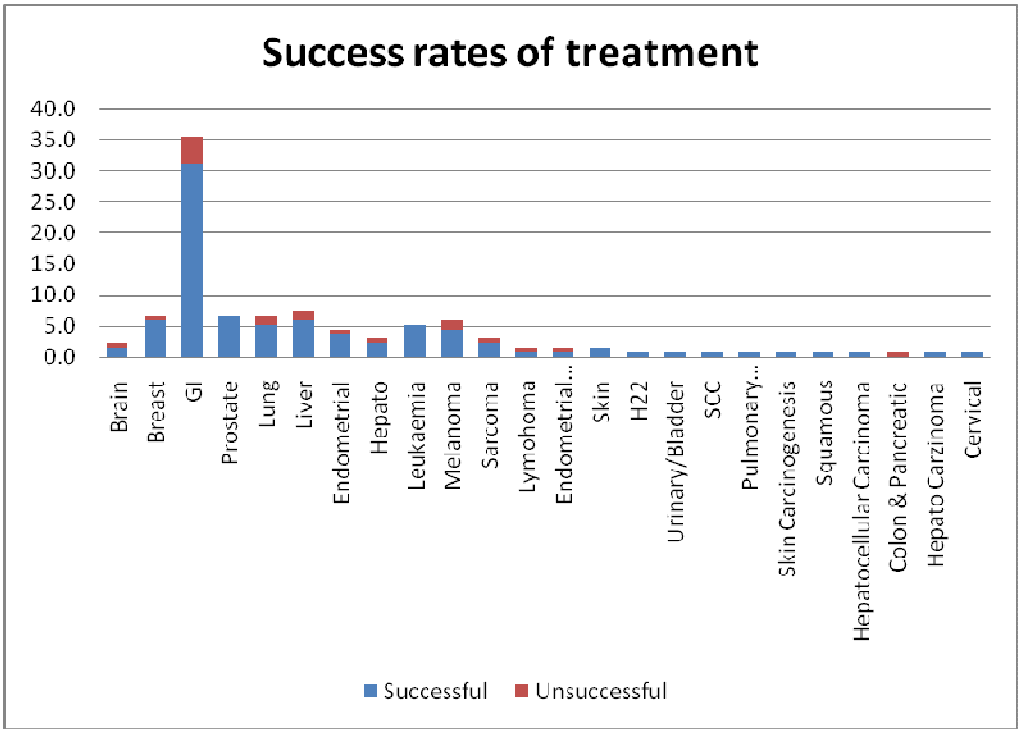
Question	Proposed answer format
What cancer type?	Breast/GI/Brain/Prostate/Lung/Other
Was the treatment successful	Yes/No
What species?	Zebrafish/Rat/Mouse
What type of model	Syngeneic/xenogeneic/Other
What cell line?	Yes/No
Any patient tissue used?	Yes/No
What was the complexity of the model	Simple/metastatic/orthotopic
Was a clinical reference of dosing used?	Yes/No

2. RESULTS

2.1 What cancer type was most studied and was the treatment successful?

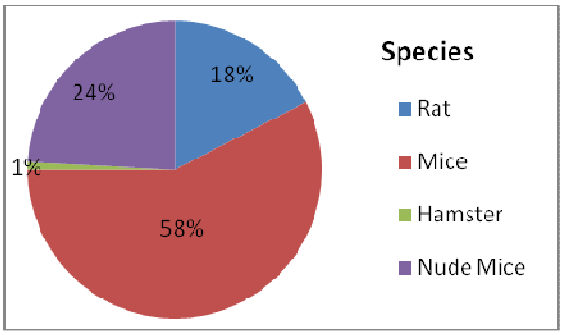
The most widely studied cancer type was GI (35%) with breast cancer, prostate cancer, endometrial cancer, liver cancer and melanoma equally studied (approx 6-7%). The CHM tested proved successful in reducing the cancer studied e.g. GI (36%)

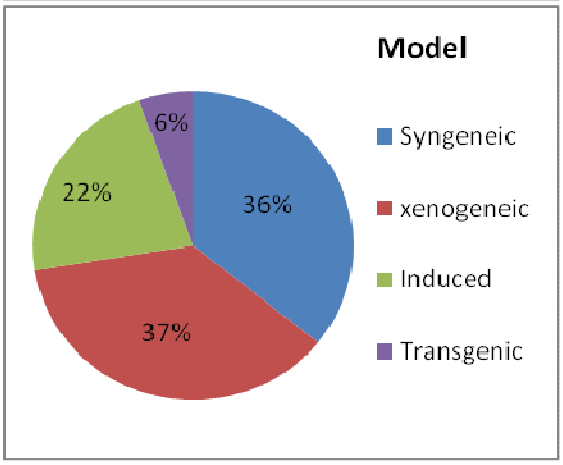




2.2 What species and strains was used and was the model synegenic or xenogeneic?

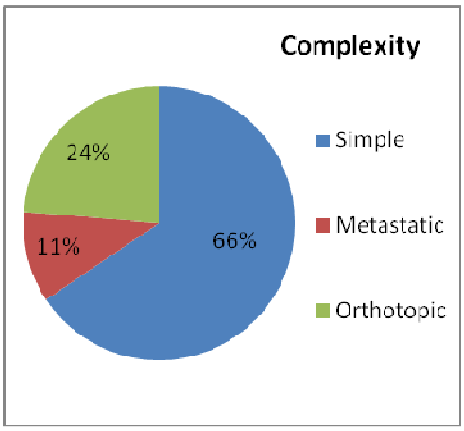
The majority of animal studies used mice (82%), with 24% being immunocompromised mice. The type of models were equally distributed between xenogenic and syngenic (36-37%), although many were also chemically-induced carcinogen models, which could also be classed as syngeneic (22%).





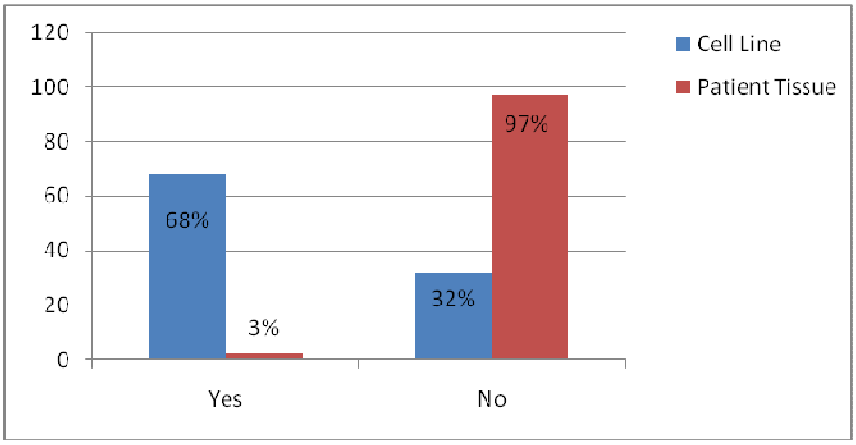
2.3 How complex are the models?

Across all the model types the complexicity of the the majority of the models was simple models (66%) e.g. subcutaneous, and the remainder were complex models such as orthotopic (24%) and metastatic (11%).



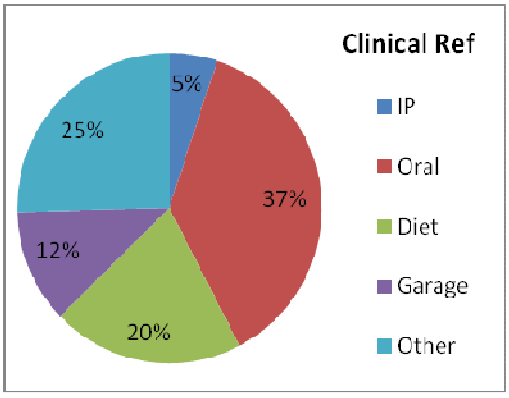
2.4 Cell lines versus patient's tissue?

The majority of studies did not use a cell line or patient material as these were most likely transgenic or chemically-induced models. For either syngeneic or xenogeneic the preference was to use a cell line rather than patient tissue (68% versus 3%).



2.5 Clinical relevance of administration route, dosage level, frequency?

CHM was mainly administered via oral route (oral gavage or diet) in the majoirty of studies (69%)



Comments on the results

At present, the animal models with the widest use in experimental therapeutics of TCM are transplanted animal tumor models and chemically-induced tumor models. The most common cancer types studied were gastrointestinal, mainly stomach and colon, followed by breast and prostate. The majority of experimental animals were either conventional or nude mice (82%) and the majority of models involved use of xenograft, syngeneic cancers or carcinogen-induced models (94% in total). The models were simple, i.e. subcutaneous implantation, mostly derived from cell lines and treated orally by gavage or via the diet (51%).The main signalling pathways involved were those associated with apoptosis and angiogenesis. Biomarkers were infrequently used with PSA being the most commonly cited. Very few details on associated toxicity were described, and, where defined, were associated with weight loss. A small number of studies (20%) compared test agent effects with Western standard of care agents and in terms of experimental design, 50% of studies used group sizes

>5, 40-50% had appropriate statistical analyses and included a relevant control, however only 14% of studies cited compliance with a regulatory authority. Variation in tumour size within experiments was not shown in 41% of studies but where shown was >10% in 34% studies and clinically-relevant treatment of established lesions were only described in 19% of papers.
Overall the quality of research was insufficient/poor in 41% of papers and good/ excellent in 9%
Use of TCM in patients, as compared with chemical compound anticancer researches, focuses on both cytotoxic action on cancer cells and improvement of immunity in the host body, or antagonism of side effects induced by conventional chemotherapy. However, one striking finding is that the animal studies of CHM in cancer only focus on the cytotoxic action, which is the same focus as studies with conventional 'Western' antineoplastic agents. Therefore the animal studies of CHM in cancer seem to not take account of the main part of the traditional approach of CHM to cancer. This may be due to the compromise of examining cancer agents on human cancer cells in vio which involve the use of immune-compromised animals allowing an incomplete evaluation of the contribution of the immune system.

Most CHM materials used for the treatment of animal models of cancer (crude herbs, dried herbs, powder, extracts, etc) were commercially prepared, but data on authentication and quality control were generally missing. In particular, it is a very frequent practice of Chinese research teams to use herbs of unknown origin, which are subjected to a variety of extraction procedures to render extracts whose composition is unknown. The non-standardized research materials 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. It is concluded from this second part of the review that there are not many papers on cancer in animal studies of CHM and they are generally published in low IF journals, possibly due to the lower IF found in phytotherapy studies but also to less stringent authentication and quality control of CHM materials and the dubious reproducibility and reliability of CHM studies.

The selection(?) of animal models for cancer research followed mostly the criteria of western medicine, lack the diagnosis from TCM syndromes. In most experimental studies, quite few signs and symptoms of animal models for cancer research were determined. The signs and symptoms described in the literature were as follows: body weight, food intake, hair, activity, faeces. Moreover, these signs and symptoms were investigated generally and commonly, but not as the evaluation or the mark of the efficacy of Chinese medicine. At present, in the experimental studies of animal models for cancer research, most researchers mainly determine the clinical efficacy of TCM through the following indicators: tumor size and weight, tumor growth inhibition, inhibitory rate of metastasis, and survival time. Despite being a large number of studies about animal models of cancer, the problem remains that generally, experimental studies are not so standardized. Therefore, the CHM scientific community should concentrate more on standardization in future studies. The diagnostic criteria of animal models for cancer research needs to be quantified and standardized, and the efficacy evaluation needs to be unified as well. And should be added the TCM syndromes,

reflecting the characteristics of Traditional Chinese Medicine: Syndrome Differentiation Treatment. Secondly, the efficacy evaluation needs to be unified as well.

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