

# Traditional Chinese Medicine Interventions for Managing Cancer Treatment Induced Side Effects in Human Patients: A Systematic Review and Meta-Analysis with Comments on Veterinary Medicine

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## ABSTRACT

Cancer is one of the leading causes of mortality in humans as well as companion animals. Commonly used conventional medical treatments such as chemotherapy and radiation are associated with significant side effects such as vomiting, nausea, fatigue, bone marrow suppression and decreased quality of life. The objective of the current literature systematic review and meta-analysis was to answer the question: Can the adverse effects of conventional cancer therapies be ameliorated by the integration of traditional Chinese medicine (TCM). Given the lack of research in veterinary oncology in this area, the systematic review and meta-analysis reviewed human studies exclusively. A total of 15 studies met inclusion criteria for meta-analysis from the initial 57 articles obtained through an internet search engine. Statistical evaluation using Stouffer's Z-scores resulted in an overall  $p$ -value of  $8.82 \times 10^{-6}$  for reduction of adverse side-effects in patients receiving acupuncture treatments and  $5.45 \times 10^{-22}$  for patients receiving Chinese herbal medicine (CHM) treatment. The marked statistical significance strongly supported the hypothesis that patients receiving TCM therapy (acupuncture, CHM) along with conventional cancer treatment (chemotherapy and radiation therapy) have significantly fewer side effects than individuals who do not receive TCM treatment. The statistically significant results of the meta-analysis demonstrate the addition of TCM to standard conventional chemotherapeutic and radiotherapy protocols reduces adverse effects associated with treatment and suggest randomized controlled studies evaluating TCM in conventional cancer treatment are warranted in human and veterinary medicine.

**Key words:** traditional Chinese medicine, oncology, cancer, side effects, acupuncture, chemotherapy, veterinary medicine

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## ABBREVIATIONS

<b>CAM</b>	Complementary and alternative medicine
<b>CHM</b>	Chinese herbal medicine
<b>CINV</b>	Chemo-induced nausea and vomiting
<b>QOL</b>	Quality of life
<b>TCM</b>	Traditional Chinese medicine
<b>TCVM</b>	Traditional Chinese veterinary medicine

Cancer is one of the leading natural causes of death in humans as well as companion animals such as dogs and cats.<sup>1,2</sup> As humans and companion animals age, the probability of developing a neoplastic process increases. Close to 45% of dogs will succumb to some type of

cancer if they live to greater than 10 years of age and 1 in 4 human deaths in the United States are attributed to cancer.<sup>1,2</sup> Conventional cancer treatment includes surgery, radiation, chemotherapy and endocrine therapy with the primary outcome to cure the disease or prolong life span.<sup>3</sup>

Chemotherapy and radiotherapy are among the most used modalities for the treatment of human oncology patients. About 28.4% of all cancer patients receive chemotherapy, with significantly more during the latest (38.7%) than those during the earliest (12.4%) stage.<sup>4</sup> The overall percentage of cancer patients receiving radiotherapy (27.3%) is similar, but the difference of percentage between the earliest (28.4%) and latest (25.4%) stages is much smaller.<sup>4</sup> These treatments, although effective for the disease, are accompanied by significant side effects in humans such as fatigue/lethargy, inappetence, vomiting/nausea, and myelosuppression.<sup>3,5-12</sup> For instance, the frequency of nausea and vomiting in

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cancer patients can cause emotional distress and in some cases dissuade the patient from continuing therapy.<sup>13</sup> Without pharmacologic intervention, the incidence of chemotherapy induced nausea and vomiting ranges from 30-90% within 24 hours of initiating chemotherapy.<sup>13</sup> These side effects greatly impact the quality of life in cancer patients.

There are a variety of anti-emetics used to treat chemotherapy-induced side effects in cancer patients. In general, these are effective for alleviating some of the clinical signs, but many patients continue to have breakthrough episodes and/or do not find complete relief. A study showed a significantly higher incidence of no chemo-induced nausea and vomiting (CINV) when the appropriate pharmaceutical interventions were used; however the control of emesis was more successful than the control of nausea.<sup>13</sup> On cancer related fatigue and lethargy, current treatments are generally limited to vitamin and supplement support as well as rest.<sup>6</sup> Myelosuppression is another side effect that is commonly associated with chemotherapeutic protocols with limited successful treatments used in human medicine aside from G-CSF (granulocyte-colony stimulating factor), which is not always used partly due to the expense.<sup>6</sup>

Traditional Chinese medicine (TCM) is a relatively new area being evaluated for amelioration of cancer treatment adverse side effects. Different from conventional medicine's uniform treatment of all individuals with the same disease diagnosis, one of the important concepts of TCM therapy is the individualized treatment based on a patient's constitution and disease pattern.

There have been reports of controlled clinical studies comparing efficacy of mitigating CINV between conventional and TCM therapies in human patients. With only a few treatments attempted to alleviate chemotherapy and radiotherapy side effects and a lack of controlled clinical studies reported in the literature for companion animals, there is little information on how traditional Chinese veterinary medicine (TCVM) therapies can help veterinary patients undergoing these conventional cancer treatments. Potential reasons for the lack of available literature in veterinary patients include lack of funding and the degree of acceptance of alternative and complimentary therapies by the veterinary community.

The overall goal of this systematic review study was to motivate future similar research in veterinary cancer patients by conducting a meta-analysis on the evidence available in human research on TCM's efficacy to mitigate CINV. Specifically, based on assessment and analysis of controlled randomized clinical studies present in current literature, this study aimed to answer the question: Can the adverse effects of chemotherapy or radiotherapy be ameliorated by integration of TCM therapy? The hypothesis was that integration of TCM with conventional chemotherapy/radiotherapy treatment would reduce clinical side effects, thus identifying potential areas of oncology research that may be useful in both human and veterinary medicine alike.

## MATERIALS AND METHODS

The initial literature search was performed by using search engines Google Scholar and PubMed with the keywords including: "traditional Chinese medicine", "TCM", "traditional veterinary Chinese medicine", "TCVM", "integrative medicine", "oncology", "side effects", and "cancer". The resulting list of articles were then screened and selected based on a review of their titles. The year of publication was limited between 1990 and 2017.

The second step was to select articles from the initial screening to be included for meta-analysis. Inclusion criteria included: (1) randomized controlled clinical trials conducted in human patients undergoing chemotherapy and/or radiation; (2) the intervention in the experimental group was integration of TCM with conventional cancer treatment; (3) TCM modalities used included acupuncture and Chinese herbal medicine either combined or separate use; (4) study participants were not limited by age, sex, or body weight; (5) outcome criteria assessed was reduction of common side effects of chemotherapy/radiation (nausea, vomiting, lethargy, fatigue, myelosuppression, overall quality of life assessment); (6) only articles published in English (studies published only in Chinese were not included); and (7) studies were published in a peer-reviewed scientific journal. Studies were excluded based on the following: (1) single case studies or case series; (2) lack of adequate control group; (3) lack of randomization; and (4) incomplete experimental data including lack of group statistical comparison.

The selection protocol for identifying studies to be included in the review and meta-analysis was organized in a stepwise fashion. Articles were initially reviewed by the first author (TR) using the described inclusion and exclusion criteria. Once potential articles were identified, they were to be independently reviewed and assessed by the coauthor (DS). The quality of each trial was assessed using the Jadad scale, which has a score 0 - 5 based on the descriptions on randomization, blinding, and withdrawals/dropouts, respectively.

The objective of a meta-analysis in systematic review research is to combine the results of independent, but similar studies to obtain an overall estimate of the statistical significance regarding the study hypothesis. One convenient way to achieve this with sufficient robustness is to apply Stouffer's Z-score method. This method first converts the *p*-value from each individual study to a Z score (inverse of normal cumulative distribution function) and then calculates an overall Z score by dividing the sum of all individual Z scores by the square root of the number of studies. The overall significance (*p*-value) can then be calculated by the normal cumulative distribution function. If the overall *p*-value is less than 0.05, the meta-analysis of the reviewed studies supports the study hypothesis: TCM modalities in conjunction with conventional cancer modalities reduces or resolves negative side effects of conventional cancer therapies.

Studies that only reported open intervals for  $p$ -values such as “ $p < 0.01$ ” or “ $p > 0.05$ ” instead of an exact  $p$ -value (as required for a meta-analysis) had a conservative approach applied to statistical calculation. For instance, a study reporting a  $p$ -value  $< 0.05$  had 0.05 used in the meta-analysis. A study reporting a  $p$ -value  $> 0.05$  had 0.99 used in the meta-analysis. This approach was applied throughout this systematic review study. All statistical analyses were performed using a commercial statistical software<sup>a</sup>.

## RESULTS

The initial literature search resulted in a total of 45 articles related to evaluation on the outcomes of TCM integrated cancer treatments. After further review, 12 additional relevant clinical studies were identified, for a total of 57 publications for possible inclusion in the meta-analysis. Among the 57 articles assessed, 20 were review articles that described integration of TCM with cancer treatments but did not report results from specific clinical

studies; 5 were case reports; 2 were survey studies on the use of complementary therapies during cancer treatments; 3 were study protocols; 5 clinical studies did not report outcomes on cancer treatment side effects; 2 were in-vitro studies, 1 did not include TCM treatments, and another 3 reported studies without a control group.

The result of the assessment found that a total of 16 independent clinical trials (13 articles) and 2 systematic review studies (2 articles) qualified for the meta-analysis (Table 1).<sup>3,6-12,14-25</sup> Among these 18 studies (15 articles), 5 reported results in acupuncture/acupressure and 13 (10 articles) were on Chinese herbal medicine (CHM). The total number of subjects receiving TCM was 1,945 vs. 1,784 control subjects (without TCM). In addition, for three studies that reported separate results on mitigating nausea and vomiting, both statistical outcomes were included in the meta-analysis. As a result, there were 6 efficacy outcomes (out of 5 studies) for acupuncture/acupressure studies and 15 outcomes (out of 13 studies) for CHM studies.

**Table 1:** Studies included in the meta-analysis\*

Authors (Year)	Cancer Treatment	TCVM Treatment	Study Design (No. of Subjects)	Adverse Events	$p$ -values*
Dibble et al. <sup>14</sup> (2000)	Chemotherapy	Acupressure	Randomized controlled (n = 17)	Nausea	$p < 0.01$
Streitberger et al. <sup>18</sup> (2003)	Chemotherapy	Acupuncture	Randomized placebo-controlled (n = 80)	Vomiting	$p = 0.82$
Tao et al. <sup>3</sup> (2016)	Unclear (standard medical care)	Acupuncture	Randomized controlled (n = 328)	Nausea and vomiting	$p < 0.0001$
Reindl et al. <sup>19</sup> (2006)	Chemotherapy	Acupuncture	Randomized crossover (n = 11)	Nausea and vomiting	Nausea: $p > 0.1$ Vomiting: $p = 0.374$
Shen et al. <sup>15</sup> (2000)	Chemotherapy	Acupuncture	Randomized controlled (n = 71)	Vomiting	$p < 0.001$
Guo et al. <sup>20</sup> (2017)	Chemotherapy	Chinese herbal medicine	Randomized controlled (n = 61)	Nausea and vomiting	Nausea: $p < 0.001$ Vomiting: $p = 0.002$
Jiao et al. <sup>21</sup> (2017)	Chemotherapy	Chinese herbal medicine	Randomized double-blinded controlled (n = 314)	Vomiting	$p = 0.004$
Wang et al. <sup>22</sup> (2016)	Chemotherapy	Chinese herbal medicine	Systematic review (N = 985)	Nausea and vomiting	$p < 0.0001$

Table 1 cont.

Authors (Year)	Cancer Treatment	TCVM Treatment	Study Design (No. of Subjects)	Adverse Events	<i>p</i> -values*
Zhang et al. <sup>6</sup> (2007)	Chemotherapy	Chinese herbal medicine	Three randomized controlled trials	Nausea and vomiting	$p = 0.11^a$ $p = 0.14^b$ $p < 0.001^c$
<sup>a</sup> Li et al., 2001 (n = 75) <sup>7</sup> ; <sup>b</sup> Yang, 2004 (n = 59) <sup>8</sup> ; <sup>c</sup> Situ et al., 2005 (n = 120) <sup>9</sup>					
Chan et al. <sup>23</sup> (2011)	Chemotherapy	Chinese herbal medicine	Randomized controlled (n = 81)	Nausea and vomiting	$p = 0.835^*$
*after 6 cycles					
Wang et al. <sup>16</sup> (2015)	Letrozole/ Tropisetron/ Chemotherapy	Chinese herbal medicine	Systematic review (n = 329)	Nausea and vomiting	$p < 0.00001$
Wu et al. <sup>10</sup> (2005)	Chemotherapy	Chinese herbal medicine	Two randomized controlled trials	Nausea and vomiting	$p = 0.015^d$ $p = 0.007^e$
<sup>d</sup> Guo, 1999 (n = 69) <sup>11</sup> ; <sup>e</sup> Xiao et al., 1998 (n = 75) <sup>12</sup>					
Tian et al. <sup>24</sup> (2015)	Chemotherapy	Chinese herbal medicine	Retrospective controlled (n = 812)	Leukopenia, neutropenia, and febrile neutropenia	$p \leq 0.005$
Yang et al. <sup>17</sup> (2014)	Gefitinib	Chinese herbal medicine	Retrospective case-controlled (n = 116)	Rash (caused by gefitinib)	$p = 0.048$
Mok et al. <sup>25</sup> (2007)	Chemotherapy	Chinese herbal medicine	Double-blind randomized controlled (n = 120)	Nausea and vomiting	Nausea $p = 0.04$ Vomiting $p = 0.22$

\**p*-values are focused on nausea and vomiting; ^ = both statistical outcomes are reported on the 3 studies that report separate results for nausea and vomiting; No. = number

The mean Jadad scale among the 18 included studies was 1.9 (SD = 1.53). Two studies scored 5; 6 studies scored 3 or better. Fifteen studies mentioned the use of randomization, but only 7 described the methods. Six studies were blinded, all with randomization but only 3 with descriptions on blinding. Only 4 studies described withdrawals and dropouts when reporting the results.

Stouffer's Z-scores from different studies with acupuncture treatment were calculated based on the reported *p*-values (Figure 1). It is worth noting that, when a study reported *p*-values for nausea and vomiting, respectively, both *p*-values were included in this meta-analysis to avoid arbitrary choices. Based on the Z-scores, the overall *p*-value was  $8.82 \times 10^{-6}$  ( $= 0.00000882$ ), which strongly supports the hypothesis that patients receiving acupuncture treatments along with their cancer treatments (chemotherapy or radiation therapy) have significantly fewer side effects than those not receiving acupuncture

treatments with their cancer therapies.

Using the same method, Stouffer's Z-scores from different studies with CHM treatment were calculated based on the reported *p*-values (Figure 2). Similarly, when a study reported *p*-values for both nausea and vomiting, respectively, both *p*-values were included in this meta-analysis to avoid arbitrary choices. Based on the Z-scores, the overall *p*-value was  $5.45 \times 10^{-22}$  which supports the hypothesis that patients receiving CHM treatment along with conventional cancer treatment (chemotherapy or radiation therapy) have significantly fewer side effects than those not receiving CHM treatment with conventional therapy. When all of the studies were combined, the resulting overall *p*-value was 0 (difference from 0 was smaller than the precision of the R software). The conclusion from this meta-analysis supported the overall study hypothesis of this systematic review study.

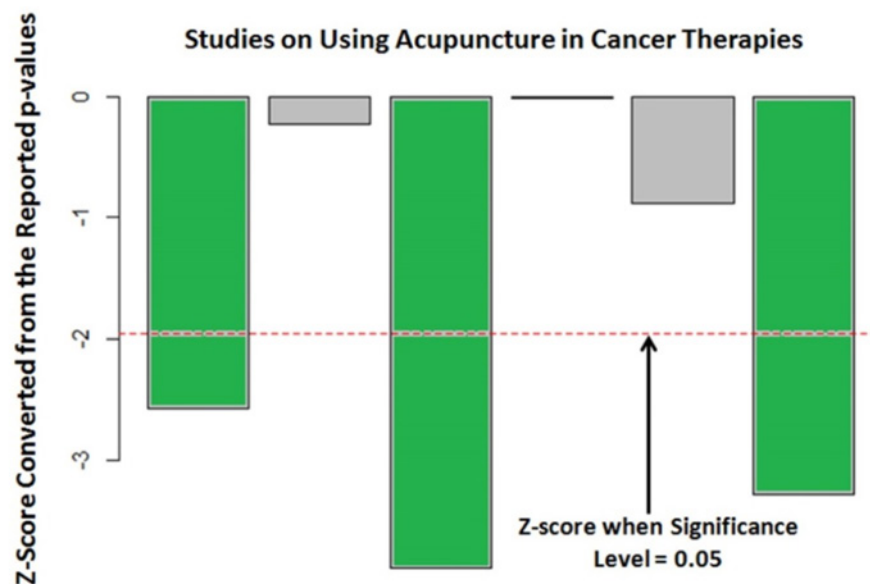
## DISCUSSION

A total of 15 articles that included 16 randomized controlled clinical trials and 2 systematic reviews with a total of 1,945 patients in the experimental groups (with TCM) and 1,784 in the control groups (without TCM) were reviewed and submitted for meta-analysis. Combining 6 statistical evaluations using Stouffer's Z-scores resulted in an overall  $p$ -value of  $8.82 \times 10^{-6}$  for reduction of adverse side-effects in patients receiving acupuncture treatments. For the meta-analysis on CHM treatment, combining 15 statistical evaluations resulted in an overall  $p$ -value of  $5.45 \times 10^{-22}$ . The marked statistical significance satisfies the hypothesis that patients receiving TCM therapy (acupuncture, CHM) along with conventional cancer treatment (chemotherapy or radiation therapy) have significantly fewer side effects than individuals who do not receive TCM treatment.

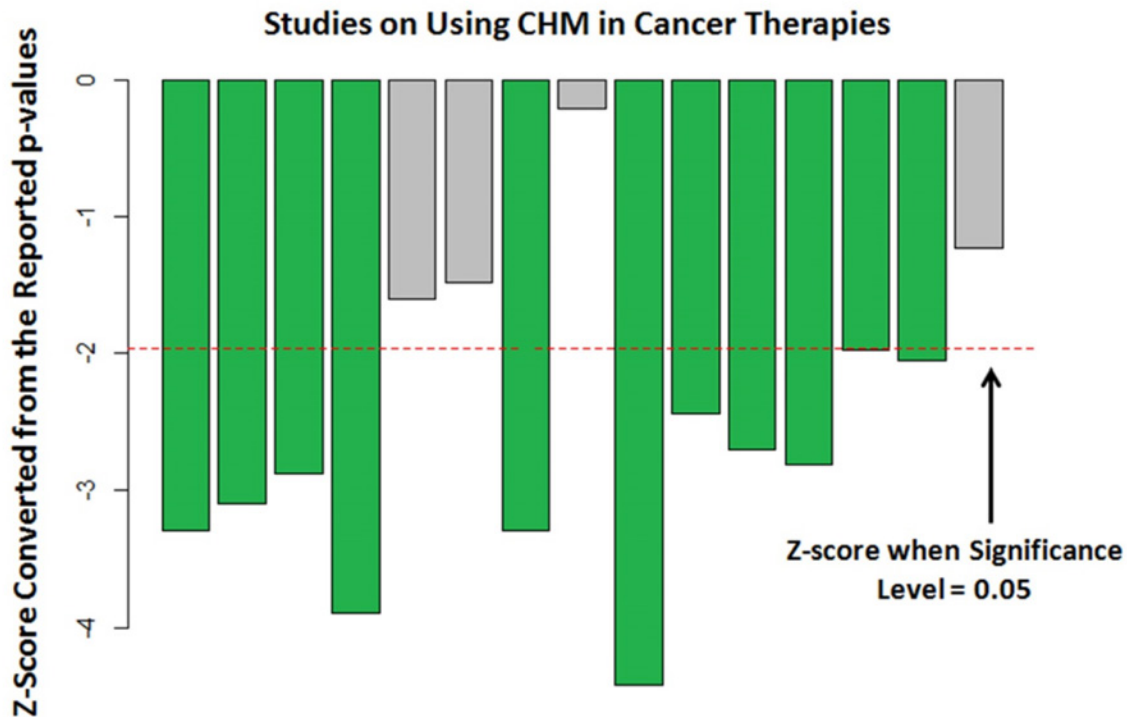
Acupuncture for oncology patients is a relatively new field of research study. Considerations for this treatment modality include efficacy and safety. When evaluating efficacy, one of the more commonly studied acupuncture/acupressure therapies for chemotherapy induced nausea was the use of acupuncture points, Pericardium 6 (PC-6) and Stomach 36 (ST-36). Dibble et al. evaluated the effectiveness of acupressure for treatment of nausea, a common side effect of breast cancer chemotherapeutic regimens which results in hesitance to continue therapy.<sup>14</sup> This study compared the frequency and intensity of nausea in women breast cancer patients undergoing chemotherapy that received regular standard of care and those receiving standard of care in addition to acupressure bilaterally at PC-6 and ST-36.

The study concluded that significant differences existed between the 2 groups during the first 10 days of the chemotherapy cycle with the acupressure group reporting less intensity ( $p < 0.04$ ) and frequency ( $p < 0.01$ ) of nausea. In a different randomized controlled clinical trial, Shen et al. investigated the efficacy of electroacupuncture for control of myeloablative chemotherapy-induced emesis.<sup>15</sup> The study concluded that there was good evidence for electroacupuncture's effect in controlling emesis, although the effect might have limited duration. When considering safety, the literature supported that this is a safe modality with a low incidence of side effects.<sup>26</sup> One paper reported the rate of minor adverse effects with dry needle acupuncture estimated to be 14 per 10,000 sessions.<sup>26</sup>

The most common herbal medications used in the clinical studies were Astragalus-based Chinese botanicals; however, there were a variety of herbal prescriptions used. Wang and colleagues conducted a systematic review study comparing treatment effects of platinum-based chemotherapy alone or with platinum-based chemotherapy plus Astragalus-based Chinese botanicals in advanced non-small cell lung cancer patients.<sup>16</sup> With the addition of TCM to treat side effects including myelosuppression, fatigue, poor appetite and nausea/vomiting; all side-effects were documented as significantly more frequent in the group of platinum-based chemotherapy alone versus the group combining the chemotherapy with Astragalus-based Chinese herbal medicine. There were no significant adverse effects associated with the herbal medications reported.



**Figure 1:** The  $p$ -value converted Z-score from different studies (5 studies; 6 statistical evaluations) reporting outcomes of acupuncture treatment reducing adverse events caused by cancer treatment; evaluations with Z-scores smaller than (more negative) or equal to the dotted line indicate statistical significance at a 0.05 level; green bars indicate studies with statistically significant outcomes and grey bars are those with insignificant outcomes.



**Figure 2:** The  $p$ -value converted Z-score from different studies (13 studies; 15 statistical evaluations) reporting outcomes of CHM treatment reducing adverse events caused by cancer treatment; evaluations with Z-scores smaller than (more negative) or equal to the dotted line indicate statistical significance at a 0.05 level; green bars indicate studies with statistically significant outcomes and grey bars are those with insignificant outcomes

There were several limitations to this study. First, most (12/18) of the studies used were unable to adequately blind patients or the physicians administering the treatments. As a result, the study outcomes were subject to bias. The second limitation was that, although some of the studies included a sham acupuncture control group, it is unclear if stimulation of non-optimal acupuncture points or locations near acupuncture points results in unexpected effects and thus potentially would confound study outcomes. Interpretation of study results was another limitation due to the lack of standardization of TCM treatment in the experimental group. This, however, is not poor study design but is the essence of TCM therapy. The selection of TCM treatment is individualized and is based on an individual's clinical signs. In addition, as an individual's condition changes, treatment is modified to accommodate those changes. Thus, some of the studies started with one herbal therapy and then switched to different herbal combinations depending on clinical signs as the patient progressed. A final limitation present in several of the studies was the conduct of the study on a specific population of people (e.g. women only, or in a specific part of the country). It is then unclear if the effects noted for a particular therapy would be similar across populations of people in different geographic areas, age group, or gender.

Given the statistically significant association between TCM therapy and reduction of cancer treatment adverse side-effects, further larger randomized controlled studies evaluating the use of TCM are warranted. The design of future studies might be able to address the lack of blinding and standardization of the current studies by using a specific herbal formula and placebo, that is produced by the same manufacturer, using a standardized dose and route of administration. Blinding of acupuncture point stimulation is always a challenge but might be addressed by adding a group that receives stimulation of the sham points only to demonstrate lack of clinical effect. As TCM and other integrative therapies are becoming more requested in the United States and other countries, more data encompassing a variety of cultures, genders, and age groups will be available (to include in studies) as well as required to continue to evaluate the use of TCM as an adjunct treatment with conventional cancer therapy. Conventional oncology treatments are also evolving (e.g. chemotherapeutic and radiation protocols, adjunctive drugs to treat side effects), which will necessitate additional research involving TCM in conjunction with the newer protocols. There are also potentials to study TCM as a primary therapy to combat neoplastic disease in patients unable to tolerate conventional chemotherapy or radiation.

As this field of study continues to grow in human medicine, there will be increasing interest in veterinary medicine to find effective and safe modalities that can be integrated with conventional oncology protocols to address adverse treatment side-effects. TCVM is suspected to be of benefit in veterinary cancer patients, but at this time, there is little evidence-based work to confirm this suspicion. High quality randomized controlled clinical studies will hopefully be performed to gather data in support of these practices and contribute to the evidence-based medicine in the veterinary literature. One additional potential consideration is to look at TCVM (herbal medications and/or acupuncture point stimulation) in conjunction with conventional cancer treatments to try to combat chemotherapy-induced neutropenia which is an adverse side-effect that can be seen in mammals.<sup>6,16,27</sup> Other study directions include investigating the addition of TCVM to combat the cancerous processes themselves rather than just the side effects of conventional treatment.

In summary, the overall goal of this systematic review study was to assess current evidence supporting TCM's effectiveness of ameliorating or reducing the adverse clinical side effects of chemotherapy or radiotherapy (primarily CINV). Despite the study limitations, the results from this meta-analysis supported the overall study hypothesis. It is the authors' hope that this review may encourage further studies evaluating the integration of TCM and TCVM in both human and veterinary oncology.

### Acknowledgements

The authors would like to thank the Chi University for their assistance with this project.

### Declaration of Interest and Funding

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this paper and the authors did not receive any specific grant of funding from any organization in the public, commercial or non-profit sectors.

### FOOTNOTES

- <sup>a</sup>. R version 3.5.2., The R Foundation for Statistical Computing, Vienna, Austria

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