EFFECT OF CURCUMIN DOSE, TREATMENT DURATION AND INTERVENTION TYPE ON TUMOR INHIBITION IN ANIMAL MODELS: A SYSTEMATIC LITERATURE REVIEW USING META-ANALYSIS TECHNIQUES

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ABSTRACT: Curcuma longa L. uses widely as a traditional medicine especially in India and China for the treatment of diabetic wounds, inflammatory, hepatic, and digestive disorders. These effects lead to the research of this plant for the treatment of chronic diseases. To assess the tumour inhibition effect of curcumin in animal models by integrating various studies into a systematic literature review (SLR) and meta-analysis. Studies of curcumin treatment in tumor-induced animal models were searched in electronic databases. The assessment of the quality of the studies included and the tumor inhibition effect used SYRCLE's Risk of Bias tool and Review Manager (The Cochrane Collaboration) software. From the 732 articles identified, only 11 studies met the selection criteria and included in the analysis. Curcumin significantly inhibited the tumor volume in the animal models in overall, and the subgroup analyses revealed that high dose, long-duration curcumin treatment, and intervention by injection have a more significant effect compared to the opposite group. Curcumin was effective in inhibiting tumor volume in animal models. The study quality and heterogeneity of the meta-analysis can probably be improved if a larger-scale bases of animal models and a well-designed study were available.

KEYWORDS: *Animal models; Curcumin; Meta-analysis; Systematic literature review; Tumor inhibition.*

1. INTRODUCTION

Cancer is also termed malignant tumors and neoplasms, denotes a large group of diseases characterized by uncontrolled cellular growth and division (Alberts et al., 2015). Abnormal cellular growth and proliferation results in a tumor. Non-invasive or benign tumors could achieve a complete cure by removing or destroying the mass. However, malignant tumors or cancer, which can invade surrounding tissues, are becoming harder to eradicate and often leads to death. According to Global Cancer Statistics, 18.1 million new cancer cases and 9.6 million cancer deaths were estimated worldwide in 2018 with lung cancer as the leading cause of cancer death (Bray et al., 2018). Cancer therapy has been going through evolution over the years, and nowadays, the most common types of cancer treatments available are surgery, chemotherapy, and radiotherapy. New alternatives such as immunotherapy, nanomedicine, and gene therapy are also currently emerging to work in a different perspective for cancer treatment (Arruebo et al., 2011). Herbal medicines is another option for cancer therapy. Various compounds in medicinal plants such as polyphenols, flavonoids, and brassinosteroids have shown promising effects in inhibiting tumor growth and thus, research should be focusing more the utilization in clinical application as these herbal medicines not only can act as a treatment alternative but also as a cancer prevention (Greenwell & Rahman, 2015). Malaysia is blessed with bioresources especially plant-based and *Curcuma longa* is among the plant listed as herbal medicine.

Curcuma longa is an erect, herbaceous perennial plant, forming dense clumps with 0.6 to 1 m high. Its rhizome is stout with carrot-turmeric odor, orange-red or golden yellow color inside. The rhizome branches with 3 m cylindrical and aromatic tubers across (Lim, 2016). *Curcuma longa* is a hygrophilous plant adapts for growth in a warm and wet tropical climate with high annual rainfall either in full sun or partial shade. *Curcuma longa* distributes in tropical Southwest India, Southeast Asia, and some areas in Africa over many centuries. It is used in dried or powdered form by boiling for several hours and then ground into powder (Lim, 2016). C. *longa* inflorescences, young shoots, and leaves uses for flavouring steamed and baked fish (Liu & Nair, 2012). It proves that *C. longa* is a multi-usage herbal plant.

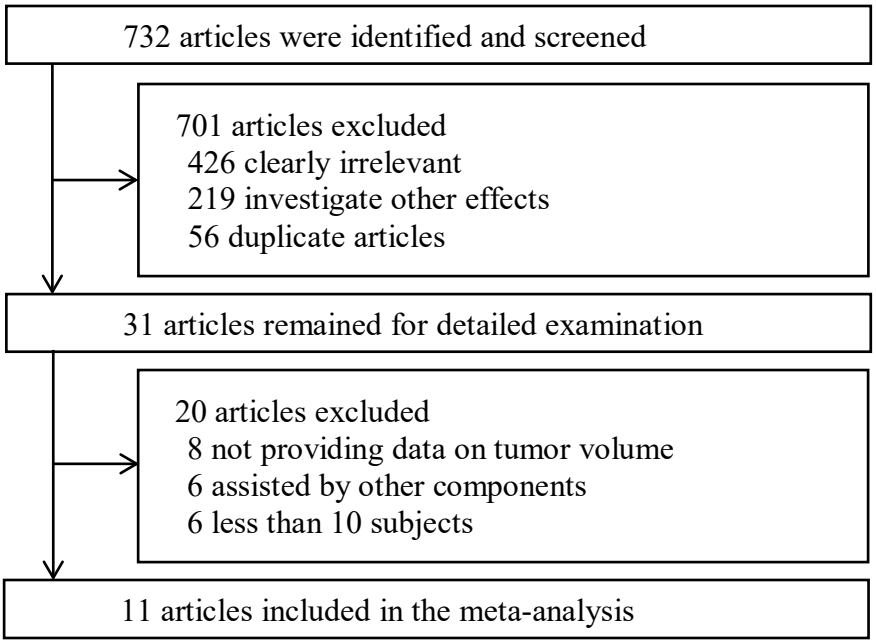

Fig. 1: Flow diagram of the literature selection.

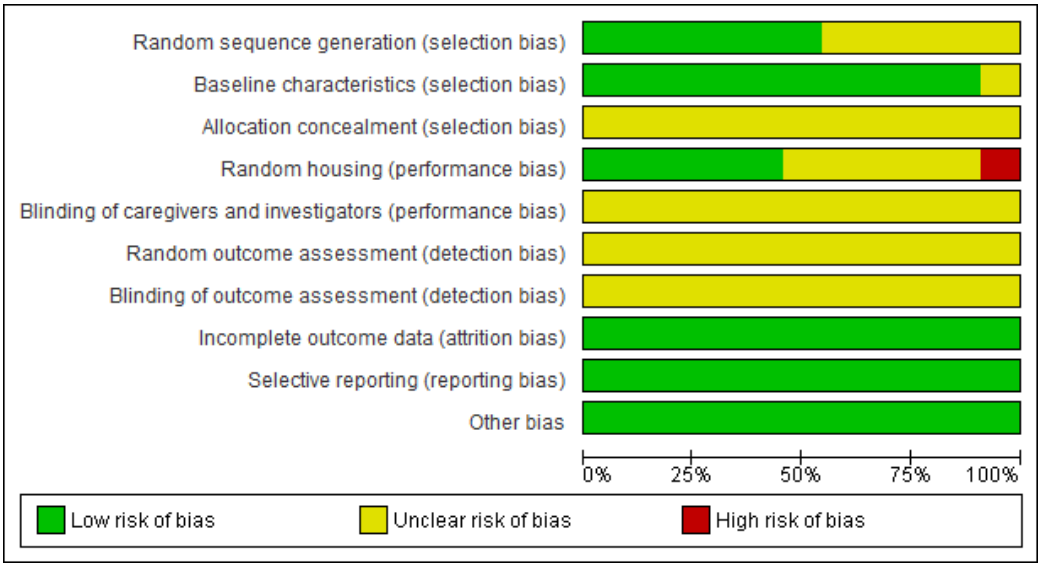

Fig. 2: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Curcumin (diferuloylmethane) is a major bioactive component found in the rhizome of *Curcuma longa* (turmeric). *Curcuma longa* L. is a member of the ginger family, Zingiberaceae, and has several synonyms such as *Curcuma domestica* Valeton, *Curcuma soloensis* Valeton, and *Curcuma brog* Valeton (The Plant List., 2013). Therapeutic effects of turmeric, which primarily stem from curcumin, have been demonstrated in various traditional applications such as hepatic disorders, diabetic wounds, sinusitis, and rheumatism (Shishodia et al., 2007). It is commonly used as an essential ingredient of

curries in Asian countries, particularly in Malaysia, India, China, and Thailand (Gupta et al., 2013). Again, C. *longa* has many usages in the Southeast Asia countries.

The chemical structure of curcumin has been proven to give numerous health benefits in the prevention and protection against various diseases. In the studies, curcumin has shown to have antimicrobial, antimutagenic, antioxidant, anti-inflammatory, and anti-diabetic properties which further investigated in its action against chronic diseases such as cancer, metabolic, cardiovascular, inflammatory, and neurological diseases (Kunnumakkara et al., 2017). Therapeutic effects of a commonly used ingredient on such chronic diseases, especially cancer, provide a research opportunity to further investigate the intervention effect in detail. Therefore, it is the purpose of this systematic review to integrate the results from various studies to determine curcumin applicability for further research works.

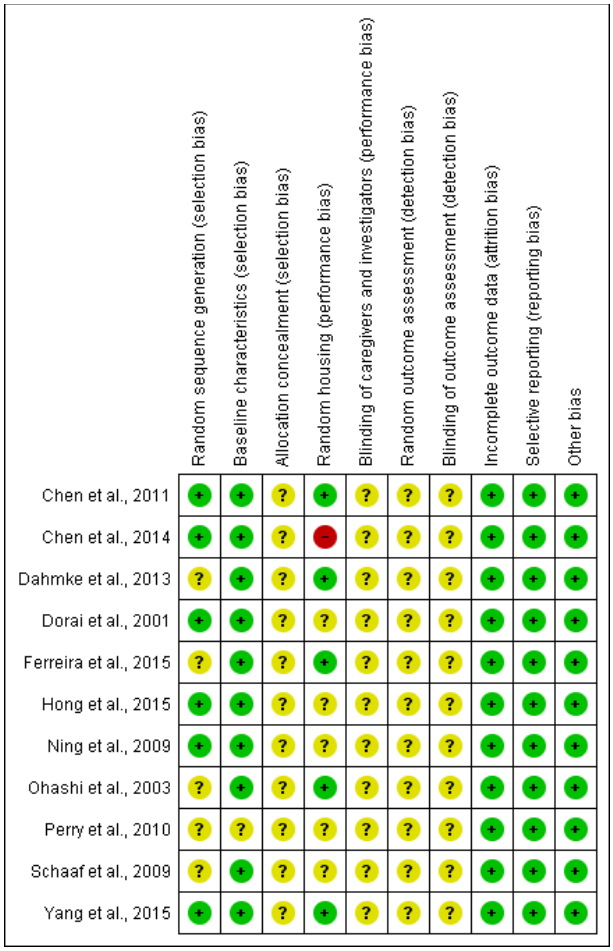

Fig. 3: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

2. MATERIALS AND METHODS

2.1 Search strategy

The literature search was conducted in September 2018 using three electronic databases, which are ScienceDirect (http://www.sciencedirect.com), Scopus (http://www.scopus.com), and PubMed (http://www.ncbi.nlm.nih.gov/pubmed/). The search terms used for the titles and abstracts focused on *in vivo* study and the full terms are (Curcuma longa OR turmeric OR Curcuma OR curcumin OR curcuminoid OR curcuminoids) AND (*in vivo*) AND (anti-tumor). The screening process included the references in the identified articles which follow the search terms.

2.2 Study selection

All the articles identified in the databases were screened for inclusion in the analysis using the following criteria:

1) *in vivo* study;
2) duration of treatment for more than two weeks;
3) no additional treatment involved;
4) the volume of the tumor for the control and treatment group were available; and
5) the subject number is not less than 10.

2.3 Data extraction and quality assessment

Table 1: Characteristics of the included studies.

Authors, publication year, country	No. of subjects	Type of cancer	Animal models	Dose	Duration
Chen et al., 2011. China	60	Melanoma	Female C57BL/6 mice with B16F10 xenograft	100 mg/kg/d (i.p.)	18 days
Chen et al., 2014. China	12	Lung cancer	Nude mice with 801D xenograft	45 mg/kg/d (i.p.)	30 days
				60 mg/kg/d (i.p.)	
Dahmke et al., 2013. Germany	13	Melanoma	Male C57BL/6 mice with B78H1 xenograft	8 g/kg/d (diet)	42 days
Dorai et al., 2001. New York	30	Prostate cancer	Male nude mice with LNCaP xenograft	2% of PICO5053 diet	Four weeks
					Six weeks
Ferreira et al., 2015. Brazil	13	Breast cancer	Female mice with MDA-MB-231 xenograft	300 mg/kg/d (i.p.)	21 days
Hong et al., 2015. Korea	20	Prostate cancer	Male Balb/c nude mice with LNCaP xenograft	500 mg/kg/thrice weekly (p.o.)	Four weeks
Ning et al., 2009. USA	20	Hepatocellular carcinoma	Male nude mice with SK-Hep-1 xenograft	100 mg/kg/d (i.p.)	16 days
Ohashi et al., 2003. Japan	24	Hepatocellular carcinoma	Female B6C3F1 mice with CBO140C12 xenograft	100 mg/kg/d (p.o.)	20 days
				200 mg/kg/d (p.o.)	
Perry et al., 2010. Canada	21	Glioblastoma	Female mice with U-87 xenograft	60 mg/kg/d (i.p.)	27 days
					37 days
Schaaf et al., 2009. Germany	12	Pituitary tumors	Male nude mice with GH3 xenograft	1 mg/mice/thrice weekly (i.p.)	Four weeks
Yang et al., 2015. China	40	Prostate cancer	Male SPF BALB/c nude mice with PC-3 xenograft	25 mg/kg/2d (i.p.)	30 days
				50 mg/kg/2d (i.p.)	
				100 mg/kg/2d (i.p.)	

This study extracted data such as authors, publication year, country, animal model, number of subjects, type of cancer, dose, duration, type of intervention, and the outcome measure which is the

tumor volume for control and treatment group including the standard deviation or standard error for statistical analysis.

The assessment of the quality of all included studies was done using the SYRCLE's Risk of Bias tool which consists of 10 items: (1) random sequence generation; (2) baseline characteristics; (3) allocation concealment; (4) random housing; (5) blinding of caregivers and investigators; (6) random outcome assessment; (7) blinding of outcome assessment; (8) incomplete outcome data; (9) selective reporting; and (10) other bias (Hooijmans et al., 2014). Three judgments were available to be chosen for each item: "yes" for a low risk of bias, "no" for a high risk of bias, and "unclear" for an unclear or unknown risk of bias.

2.4 Statistical analysis

The meta-analysis was conducted according to Hui et al., (2018) using Review Manager Version 5.3 (The Cochrane Collaboration) software to establish Forest Plots with the standardized mean difference (SMD) as the effect measure for the tumour volume. Random effects model was used for the analysis because of the expected heterogeneity using I^2 as the measure. Subgroup analysis for the influences of the dose, treatment duration, and intervention type was performed to determine the potential causes of heterogeneity.

3. RESULTS

3.1 Description of studies

The literature search using electronic databases resulted in a total of 732 articles identified among which 701 were excluded after the title and abstract screening because 426 of the studies were not related to this systematic review, 219 studies were excluded because they investigated other effects of curcumin, not anti-tumor effect, and the rest were duplicate articles. The meta-analysis maintained 11 articlesafter the second phase of full-text screening based on the selection criteria. Figure 1 shows details of the screening process.

From the 11 included articles, 17 groups of studies with a total of 298 subjects, ranged from 12 to 60 in each study, were involved in the meta-analysis. All studies used mice as their animal models, induced with seven different types of cancer, which are melanoma, glioblastoma, hepatocellular carcinoma, pituitary tumors, lung cancer, prostate cancer, and breast cancer. The dose and duration of curcumin treatment received by the subjects through either intraperitoneal injection, oral or diet intervention varied from 1 mg to 8000 mg and 16 days to 42 days, respectively. Table 1 summaries all the included studies after a systematic review process.

The risk of bias assessment of the 11 studies included in this systematic review (Figures 2 and 3) shows that six out of the eleven studies stated random allocation sequence of the animals; however, none of them reported the method of randomization. Besides, allocation concealment, blinding of caregivers and investigators, and blinding of outcome assessment was also not reported in all studies. Based on the assessment, it was determined that attrition, reporting, and other bias to be at low risk for all the studies. Only one study has a high risk of bias for random housing, and for the rest of the studies, half of them were low risk, and the other half was an unclear risk of bias. Therefore, most of the studies are suitable as review samples because they have low bias.

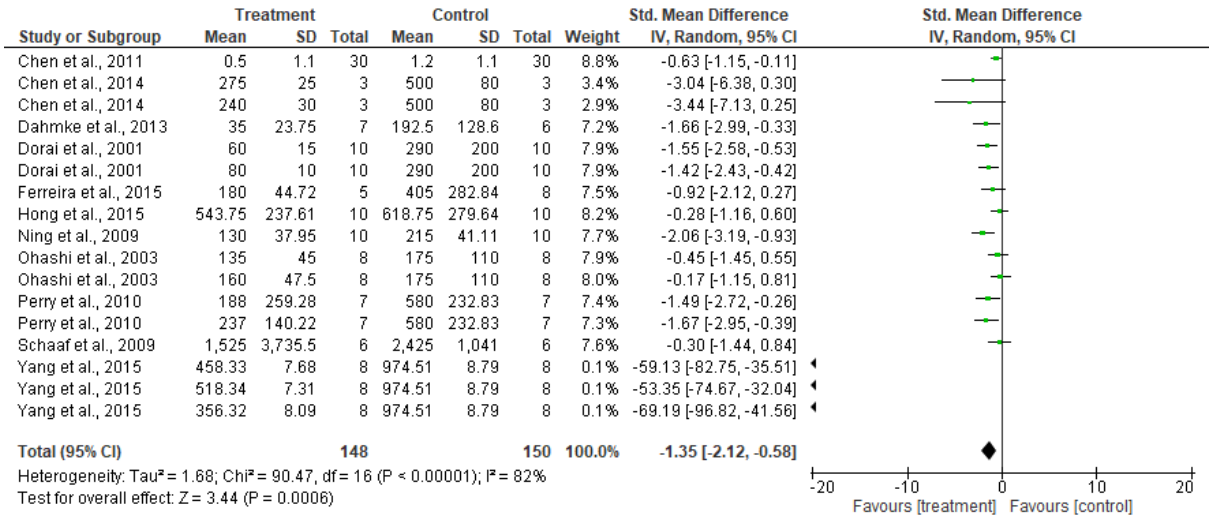

Fig. 4: Meta-analysis of the effect of curcumin on the tumor volume

3.2 Effects of curcumin on tumor volume

When compared to the control groups of the 17 studies, ten studies showed a significant decrease, and none showed a significant increase in tumor volume after treated with curcumin (Figure 4). Furthermore, the overall results revealed that curcumin intervention had a significant inhibiting effect on tumor volume (SMD -1.35[-2.12, -0.58]; n=17) but with quite high heterogeneity (I^2=82%).

The studies divided all cases into separate subgroups based on the curcumin treatment dose, duration, and intervention type to investigate the influence of these three parameters on the tumor inhibition effect of curcumin. The studies categorized cases into a high-dose subgroup when curcumin dose given is more than 1000 mg/day and long duration subgroup when a treatment duration of more than 30 days. For the dose subgroups, the effect of high dose curcumin treatment (SMD -1.52[-2.16, -0.89]; n=3) seemed to be larger than low dose treatment (SMD -1.37[-2.34, -0.40]; n=14) as shown in Figure 5. Heterogeneity levels significantly decreased in the subgroup analysis of high dose treatment (I^2=0%) while still high heterogeneity level was observed in the subgroup of low dose treatment (I^2=85%). While for duration subgroups, extended duration treatment group (SMD -4.59[-7.51, -1.67]; n=8) seemed to be affected by curcumin more than the short duration treatment group (SMD -0.79[-1.18, -0.40]; n=9) as shown in Figure 6. However, heterogeneity was higher in the extended duration treatment group (I^2=90%) than the short duration treatment group (I^2=33%). Lastly, the analysis on the influence of intervention type revealed that the intervention by injection showed the highest effect (SMD -2.12[-3.56, -0.68]; n=11) compared to diet intervention (SMD -1.52[-2.16, -0.89]; n=3) and oral intervention (SMD -0.30[-0.84, -0.25]; n=3) as shown in Figure 7. However, diet and oral intervention subgroups reduced heterogeneity (I^2=0%), while intervention by injection subgroup did not change high heterogeneity level (I^2=88%).

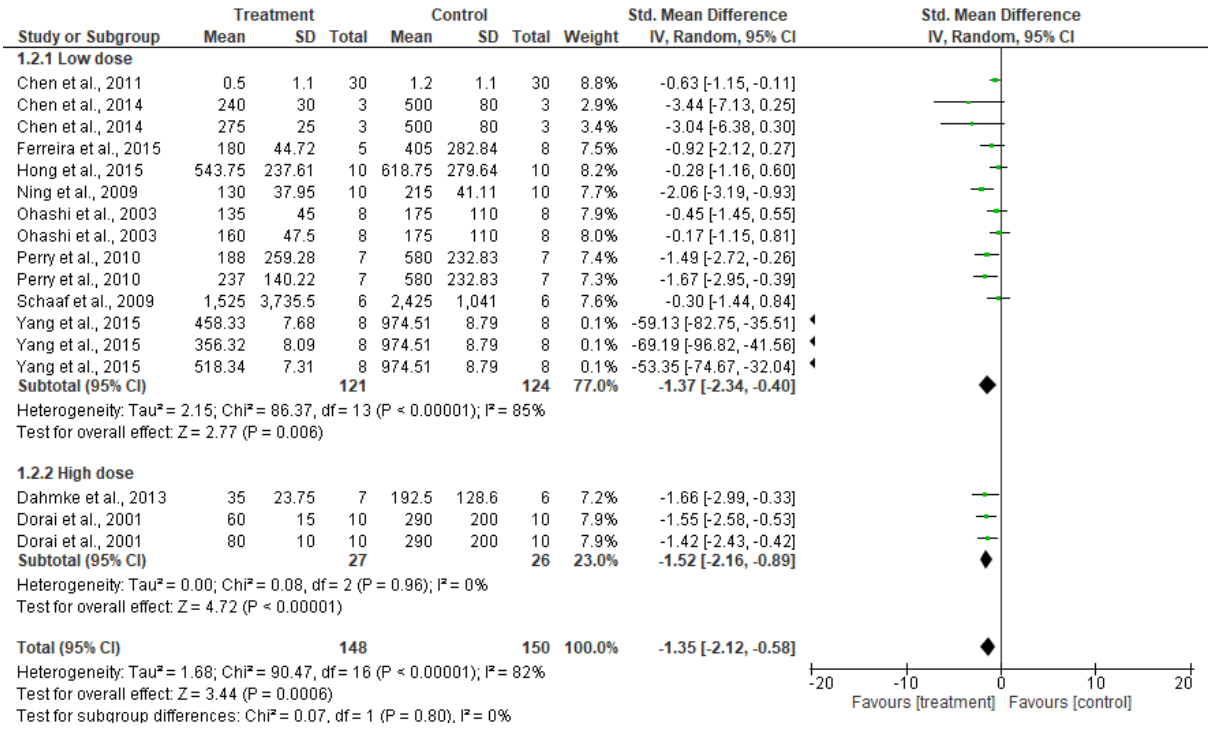

Fig. 5: Influence of the dose on the tumor inhibition effect of curcumin

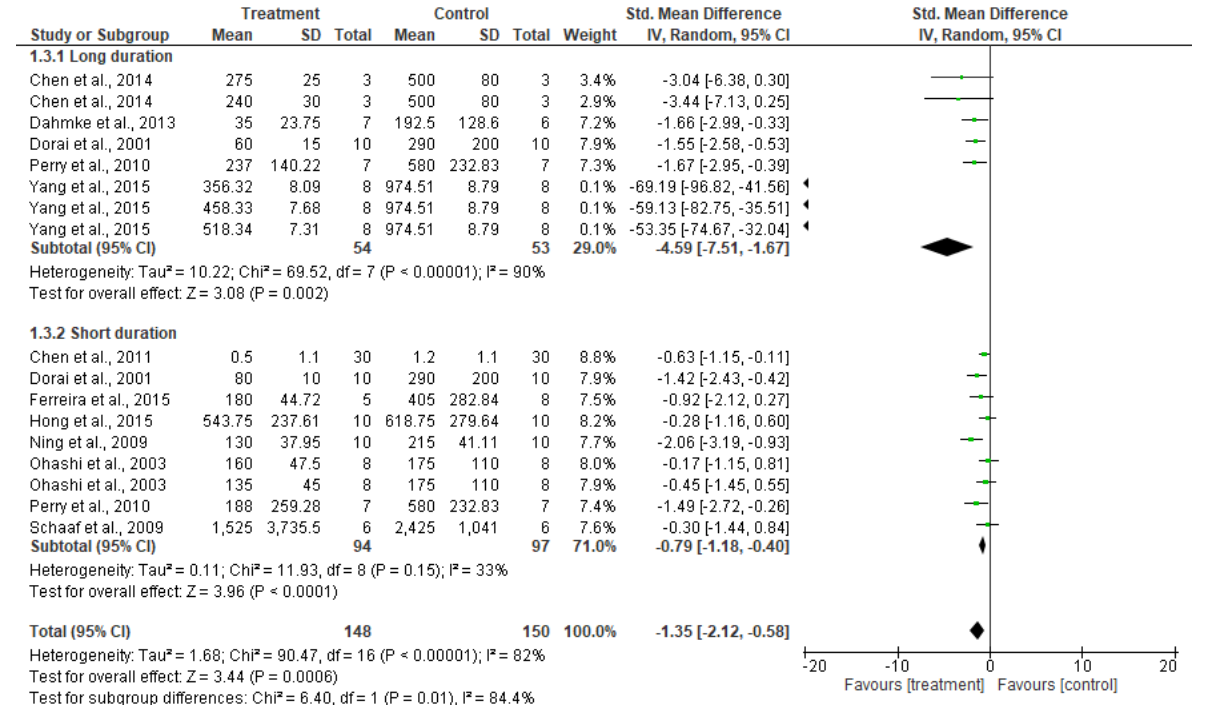

Fig. 6: Influence of the treatment duration on the tumor inhibition effect of curcumin

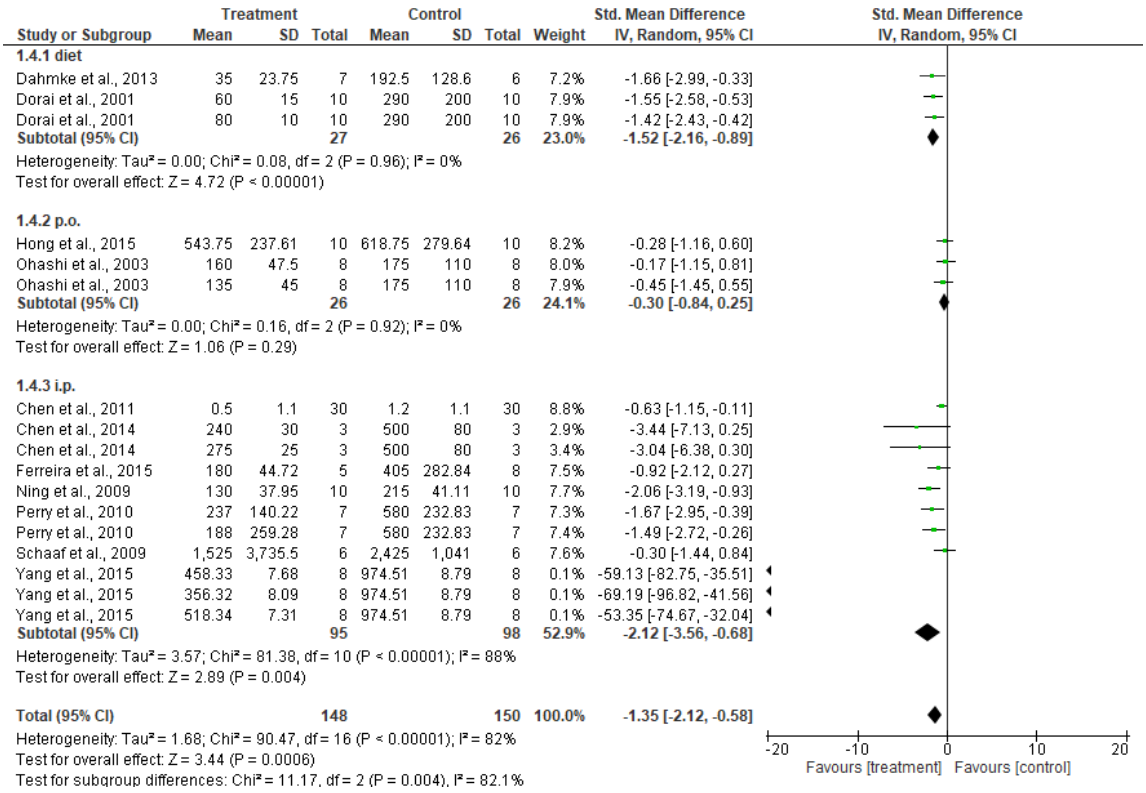

Fig. 7: Influence of the intervention type on the tumor inhibition effect of curcumin

4. DISCUSSION

This systematic review and meta-analysis were performed to assess the effect of curcumin on tumor inhibition in animal models. The overall analysis of the effect showed that the use of curcumin was associated with a significant inhibitory effect (SMD -1.35[-2.12, -0.58]; n=17) on tumor volume, compared to the untreated group. Besides, subgroup analysis of curcumin dose, duration, and intervention type revealed that high dose (Bayet-Robert et al., 2010; Dhillon, 2008; Kanai, et al., 2011; Vadhan-Raj, 2007) , long duration (Sharma et al., 2001; Sharma et al., 2004; Cruz-Correa et al., 2006; Ide et al., 2010), and intervention of curcumin by injection have a more significant effect than the different subgroups.

Dysregulation of multiple cell signaling pathways resulting from DNA mutations are responsible for carcinogenesis process and has been a focus in drug development (Wagener et al., 2017). Curcumin has been reported to regulate tumor factor expression *in vivo* through multiple pathways, unlike currently available drugs for the treatment of cancer which are mostly based on a single target modulation (Yang et al., 2015). Several factors that are implicated in carcinogenesis such as nuclear factor kappa B (NF-κB), activating protein-1 (AP-1), signal transducer and activator of transcription protein (STAT3), and Notch 1 were suppressed by curcumin thus inhibit the signalling pathways associated with the factors as reported in previous studies (Ning et al., 2009). According to Yang et al. (2015), curcumin regulates the cell cycle, oncogenes, tumor suppressor genes, and their protein expression for the induction of cell apoptosis, which leads to tumor inhibition effect.

Another mechanism in focus for tumor prevention and treatment is the angiogenesis process which is responsible for the growth and progression of cancer cells (Perry et al., 2010). Angiogenesis, which leads to the formation of new blood vessels enables cancer cells to get nutrients and oxygen for cell proliferation, hence increasing the tumor size. Angiogenic factors stimulate this process and curcumin can down-regulate several angiogenic factors expressions such as angiostatin, angiogenin, and angiopoietin through the inhibition of matrix metalloproteinase (MMP)-9 and vascular endothelial

growth factor (VEGF) expressions making curcumin a potential anti-angiogenic therapy for tumor treatment (Ferreira et al., 2015).

The development of cancer is also contributed by epigenetic alterations, as suggested in contradictory evidence (Esteller, 2008). Epigenetics are heritable changes in gene expression without changes in the DNA sequence through DNA methylation, histone modifications, and microRNA (miRNA) (Lee et al., 2013). Lee et al. (2013) reported that curcumin has potential regulatory effects of restoring abnormal epigenetic alterations by modifying DNA methylation of cancer-related genes and inhibiting histone deacetylases (HDACs) and miRNAs which helps in the inhibition of tumor growth.

The review also identified that the effect of high dose curcumin treatment seemed to be larger than low dose treatment (Figure 5), long-duration treatment group seemed to be affected by curcumin more than the short duration treatment group (Figure 6) and intervention by injection showed the highest effect compared to diet intervention and oral intervention (Figure 7). High dose, long-duration treatment, and intervention by injection are required may be due to low curcumin bioavailability and needs a high dose, more extended time in reaching optimal effect. Intervention by injection also helps in improving curcumin bioavailability when it is introduced directly to the blood vessel (Tønnesen et al., 2002; Anand et al., 2007).

Curcumin was reported to have limited distribution in the body tissues, low serum concentration indicating poor absorption, high rate of metabolism, and rapid elimination from the body which all lead to the problem of poor bioavailability (Anand et al., 2007). For oral administration, curcumin is poorly absorbed from the gastrointestinal tract and subsequently metabolized extensively within the gut and liver to glucuronide and glucuronide/sulfate conjugate detected in the plasma (Asai & Miyazawa, 2000). These two processes of orally administered curcumin in the body suggested that intervention by injection may result in more curcumin or curcumin metabolites in the plasma since it does not involve absorption process that reduces the level of curcumin from the initial intake in blood and other tissues.

Besides, intraperitoneally injected curcumin undergoes reduction into dihydro curcumin and tetrahydrocurcumin hepatically and then converts further to monoglucuronide. The metabolites, which are curcumin glucuronide, dihydro curcumin-glucuronide, tetrahydrocurcumin-glucuronide, and tetrahydrocurcumin were reported as the primary metabolites of curcumin (Pan et al., 1999). Figure 8 shows the graphical representation of the metabolism process of orally administered and intraperitoneally injected curcumin.

Rapid metabolism and elimination of curcumin from the body, as reported by Ireson et al. (2002) suggested that curcumin should be consumed regularly and continuously for more effective prevention or treatment. They found that a low dose injection of curcumin eliminated from the plasma within 1 hour while a higher dose of orally administered curcumin was found at levels near the detection limit. Thus, for a better tumor inhibition effect, high dose of curcumin with a longer duration of administration by injection is recommended.

In conclusion, curcumin has shown compelling effects in tumor prevention and treatment through several mechanisms, which are inhibition of aberrant signaling pathways, anti-angiogenesis, and restoration of epigenetic alterations. This systematic review of 17 animal studies suggests the tumor inhibition potential of curcumin with significant results. The study quality and heterogeneity of the meta-analysis can probably be improved if a larger-scale of animal models and a well-designed study were available. A higher dose and longer duration of curcumin treatment are significant factors, and most importantly, no dose-limiting toxicities reported in most studies. For human consumption, the low bioavailability of curcumin may be the obstacle; therefore, the efficient delivery system is a requirement when applying curcumin for the treatment of the tumor. These substantial benefits of curcumin could play a part in further clinical development for cancer chemoprevention.

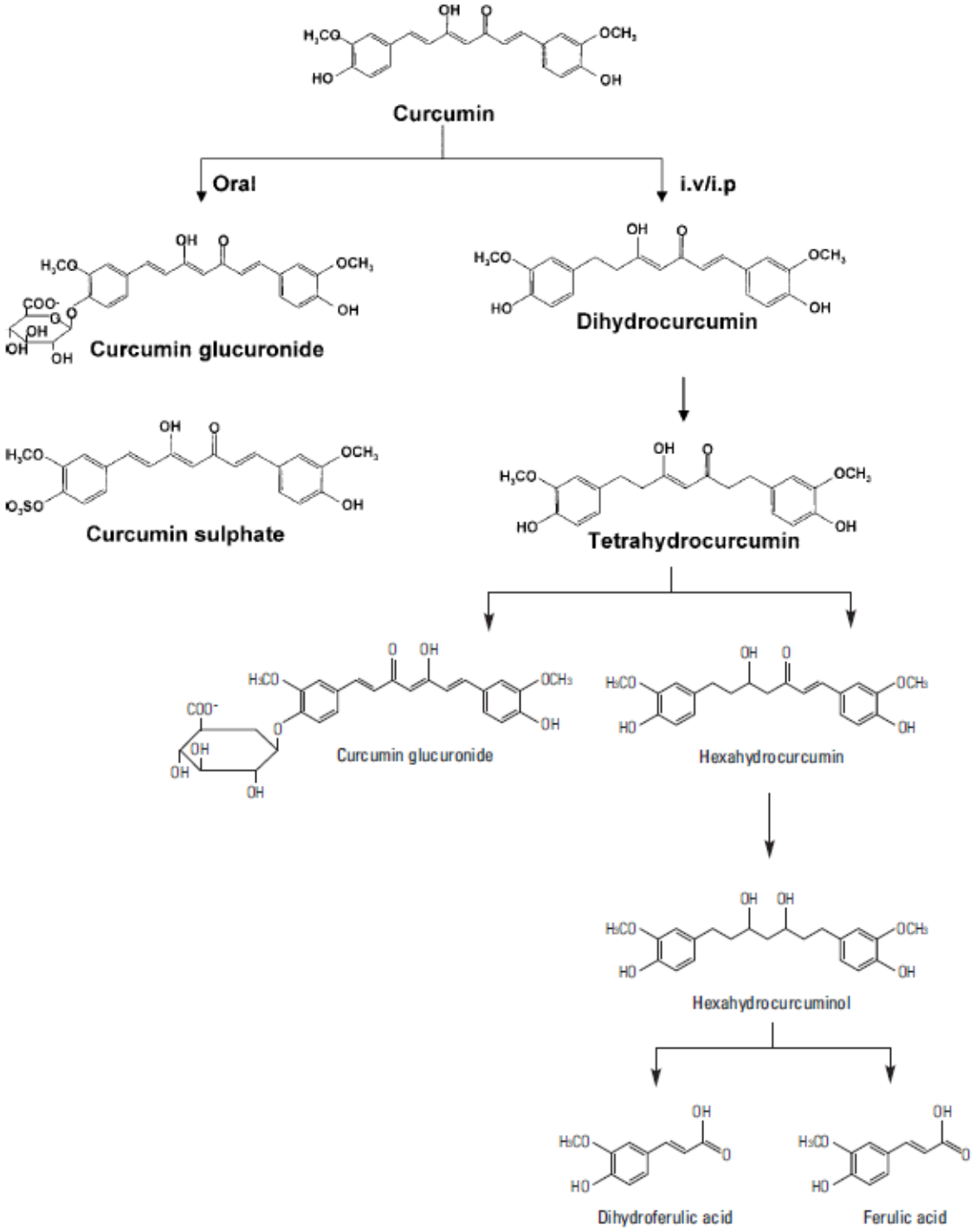

Fig. 8: Metabolism of Curcumin (modified from Anand et al., 2007 and Prasad et al., 2014)

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Conflict of Interest
There is no conflict of interest in this work.

Authors Contribution

Arina is the postgraduate student for this study and drafts the manuscript, while Azura serves as the supervisor and do all the reviewing of this paper.

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