Does curcumin improve liver enzymes levels in NAFLD? A systematic review, meta-analysis and meta-regression

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Complete List of Authors:	Aragón-Vela, Jerónimo; University of Jaén, Department of physiology SANCHEZ OLIVER, ANTONIO JESUS; University of Loyola Andalusia - Granada Campus Rodriguez Huertas, Jesus. F; University of Granada Casuso, Rafael A; Universidad Loyola Andalucia
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Does curcumin improve liver enzymes levels in NAFLD? A systematic review, meta-analysis and meta-regression.

Jerónimo Aragón-Vela PhD [1]; Antonio Jesús Sánchez Oliver PhD [2]; Jesús R. Huertas PhD [3]; Rafael A. Casuso PhD[#4]

[1]Department of Health Sciences, Area of Physiology, University of Jaen, Spain; [2]Departamento de Motricidad Humana y Rendimiento Deportivo, Facultad de Ciencias de la Educación, Universidad de Sevilla, 41004 Sevilla, Spain; [3]Institutes of Nutrition and Food Technology, Department of Physiology, University of Granada, Spain. [4]Department of Health Sciences, Universidad Loyola Andalucía, Spain

Corresponding author: rcasuso@uloyola.es

Running head: Curcumin and NAFLD

ABSTRACT

The aim of this meta-analysis is to investigate the sources of heterogeneity in randomized clinical trials (RCTs) examining the effects of curcumin supplementation on liver aminotransferases in subjects with non-alcoholic fatty liver disease (NAFLD). We conducted a systematic search of the PubMed, SCOPUS, and Web of Science databases for RCTs and identified 15 studies (n = 835 subjects). We used random-effects models with DerSimonian-Laird methods to analyze the serum levels of ALT and AST enzymes. Our results indicate that curcumin did not affect serum ALT, but it did reduce AST levels. Notably, both outcomes showed high heterogeneity ($p < 0.01$). Subgroup analysis revealed that adding piperine to curcumin did not benefit aminotransferase levels in NAFLD patients. Additionally, we found a negative correlation between the duration of the intervention and the relative (mg/kg/day) curcumin dose with the reduction in liver aminotransferases. In summary, the sources of heterogeneity identified in our study are likely attributed to the duration of the intervention and the relative dose of curcumin. Consequently, longer trials utilizing high doses of curcumin could diminish the positive impact of curcumin in reducing serum levels of aminotransferases in patients with NAFLD.

Key words: aminotransferases, non-alcoholic fatty liver disease, piperine, obesity, polyphenol.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a globally prevalent liver disorder, characterized by hepatic steatosis, which entails the accumulation of lipids within hepatocytes in the form of micro and macro vacuoles [1]. The pathogenesis of NAFLD encompasses a spectrum of pathological conditions ranging from simple steatosis to steatohepatitis, along with varying degrees of fibrosis and cirrhosis [2]. The worldwide prevalence of NAFLD ranges from 20% to 30% in Western countries and is associated with age [3,4]. NAFLD represents a significant health concern due to its linkage with the risk of developing liver cirrhosis, liver cancer, and an elevated risk of cardiovascular diseases and solid neoplasms [5]. Therefore, the quest for a safe, effective, and affordable approach to ameliorate NAFLD and associated diseases is a focus of intense research.

Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are common biochemical markers used to characterize hepatocyte integrity [6]. Some nutraceuticals have been proposed to ameliorate serum aminotransferases levels in NAFLD [7]. Of them, curcumin, a polyphenol found in turmeric, have shown a robust beneficial effect due to its antioxidant and anti-inflammatory activity in the liver [7,8]. In fact, several meta-analyses of randomized clinical trials (RCT) have shown that curcumin supplementation can decrease serum aminotransferases levels [9–16]. Notably, the most recent meta-analysis of RCT showed that while curcumin can decrease ALT and AST serum levels in NAFLD, there is a considerable (I^2 ~80%) between-study heterogeneity [17].

The Cochrane Handbook for Systematic Reviews defines heterogeneity as any kind of variability among studies in a systematic review. In this regard, I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. A high heterogeneity has been proposed as $I^2 > 75\%$, which needs to be

further explored [18]. A recent umbrella meta-analysis used subgroup analysis to investigate heterogeneity among meta-analysis and found that curcumin dose and length can be a potential source of heterogeneity [19]. In fact, this study suggested that lower doses may have more impact in reducing aminotransferases levels. This is in line with another meta-analysis showing that curcumin (C) but not C + piperine (C+P) supplementation decrease serum ALT and AST levels in NAFLD [17], as piperine can increase curcumin's bioavailability in humans [20]. However, when clinical and methodological aspects of the results can be defined a priori; the study of the heterogeneity should also examine the relationship between the a priori defined moderators and effect size of the intervention [18].

Acknowledging that prior meta-analyses may not have comprehensively examined potential sources of heterogeneity in RCTs, the present study aims to perform a meta-analysis and meta-regression with two a priori chosen moderators—length and dose—on the effects of curcumin on ALT and AST levels in NAFLD. Moreover, as adding piperine is known to increase curcumin bioavailability, we will further study the distinct effects of studies administering only curcumin versus those combining curcumin with piperine (C versus C+P). Our study will help address critical gaps in the current understanding of curcumin treatment effects, potentially guiding more effective therapeutic interventions for NAFLD.

METHODS

Experimental approach to the problem

The study methodology follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [21]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database, with the following record CRD42023398873. The databases of PubMed, Web of Science and

Scopus were systematically searched for eligible articles from January 01, 2000, to March 10, 2023. The PICO framework is as follows: population: non-alcoholic fatty liver disease subjects, intervention: curcumin supplementation or curcumin + piperine, comparison: pre intervention vs post intervention; outcomes: alanine aminotransferase and aspartate aminotransferase. Any study on patients diagnosed with NAFLD (≥ 18 yr) with an experimental group composed of curcumin with or without piperine. Only studies published in English were included. The following search strategy was used: ("NAFLD" or "nonalcoholic fatty liver disease" or "NAFL" or "nonalcoholic fatty liver" or "NASH" or "steatohepatitis" or "hepatic steatosis") and ("polyphenol*" or "phytochemical*" or "phenol*" or "curcumin" or "curcuminoids" or "turmeric" or "piperine"). In order to identify missing studies, each selected study was individually scrutinized by clicking on the "cited" and "similar" tabs of the databases.

Study selection

The selection of the studies was independently performed by two reviewers. Studies were screened based on their titles and abstracts. In the case that a study abstract reported a study reported a protocol of curcumin supplementation with/without piperine in patients with NAFL, the full text was evaluated, as the control group could meet the inclusion criteria. Discrepancies during the study selection were resolved by consensus and/or by a third author opinion. The original search yielded 267 studies (SCOPUS= 162; WOS= 61; PubMed= 44), and after deduplication and screening 27 studies were independently read and reviewed. A total of 15 studies were included for qualitative and quantitative analysis (Figure 1). Studies involving animal subjects were excluded, as were those incorporating other forms of supplementation or additional physical activity alongside curcumin/piperine supplementation. Additionally, only studies published in English were eligible for analysis. Concerning inclusion criteria, eligibility was limited to studies

featuring a control/placebo group. Moreover, only research focusing on subjects diagnosed with NAFLD was considered.

Data extraction

The following data was extracted by two researchers independently: number of subjects, sex, age, BMI, body mass, intervention length (weeks), and serum liver ALT and AST (Table 1). We choose these two enzymes as they were the most commonly reported liver markers and gave us the opportunity to do a robust meta-regression where at least 10 studies are needed [22]. We also extracted the curcumin dose (mg/day) reported in each study as well as baseline mass (kg) of the participants, and the relative daily dose (mg/kg/day) was calculated. However, two studies [23,24] did not provide the initial body mass of the subjects. As inclusion criteria we have only considered those clinical trials with a supplementation period longer than two weeks. We identified an article studying resistance training intervention with/without curcumin [25]. In this case we only included the data of the control group and the curcumin intervention without resistance training. Where data were not presented in text or table and authors could not be reached, data were extracted using WebPlotDigitalizer [26]. Any discrepancies between reviewers were resolved by consensus.

Data synthesis and analysis

All the analysis were performed using the metafor package of R software [27]. Meta-analyses were performed using random-effects models with the DerSimonian-Laird method to evaluate the effect of supplementation in patients with NAFLD. This approach was chosen because it accommodates the expected variability between study outcomes, providing a more accurate estimation when studies are not homogenous. The DerSimonian-Laird method, specifically, is utilized to estimate the between-study

variance, thus allowing for the integration of diverse study results while acknowledging differences in study design and population. The change in mean and change in standard deviation (ΔSD) was recorded for each treatment (i.e. curcumin and placebo) and outcome. When ΔSD was not reported we calculated it assuming a correlation coefficient of 0.7 as previously suggested [28].

$$\Delta SD = \sqrt{(SD_{pre}^2 + SD_{post}^2 - 2 \times corr \times SD_{pre} \times SD_{post})}.$$

Effect sizes are presented as mean difference (MD) and 95% CIs or standardized mean difference (SMD) and 95% CIs when the outcome has non-comparable scales. As piperine co-supplementation can enhance curcumin bioavaility [20]. A subgroup analysis was performed to compare the effects between those studies using C and that using C+P. This analysis allows for a direct assessment of whether the addition of piperine enhances the efficacy of curcumin treatment in NAFLD patients by isolating the impact of the combination from studies using only curcumin. In addition, the intervention length (weeks) and the relative daily dose (mg/kg/d) of curcumin were chosen as *a priori* moderators for the meta-regression. By incorporating these moderators, the meta-regression allows us to examine the impact of varying treatment durations and dosages on patient outcomes, providing a more nuanced understanding of how curcumin works under different clinical conditions.

Understanding the optimal dosage of curcumin for treating elevated serum ALT and AST levels in NAFLD is critical for clinical efficacy. To explore the potential non-linear relationship between curcumin dosage (mg/kg/day) and its effects, fractional polynomial modeling was employed. This method allows for the detection of complex dose-response patterns that may not be evident under linear assumptions. Furthermore, by plotting the effect sizes of ALT and AST against the curcumin dosage and conducting segmental

regression analyses, we aimed to identify any breakpoints in the dose-response curve. These breakpoints indicate dosages at which the incremental benefit of curcumin may change, thus helping to establish clinically effective dosing recommendations. Data around these breakpoints were analyzed and are presented as mean ± standard deviation (SD). The R software package was employed for executing this analysis and for the creation of the corresponding figures.

Heterogeneity and Risk of Bias

Heterogeneity was reported as the I^2 value and the prediction interval derived from Tau and Cochran Q. Following the Cochrane Handbook recommendations, heterogeneity (I^2) was classified into low (0-40%), moderate (40-75%) and high (75-100%) [18]. In addition, multiple sensitivity analyses were performed to determine if any of the results were influenced by the studies that were removed. Risk of bias was assessed using visual inspection of Funnel plots and accompanying Egger's Tests using the metafor package [27]. The Critical Appraisal Checklist for Case Control Studies or RCT of the Faculty of Health and Medical Sciences at the University of Adelaide, South Australia [29] was used to evaluate bias in studies (RAC and JAV). The checklist consists of 8-13 items relating to title, abstract, introduction, methods, and results and discussion sections of articles. However, not all items were applicable in every study. Therefore, quality scores were calculated both as total of points and as percentage of the applicable items (Table 2).

RESULTS

Study characteristics.

Details on participants and outcomes are detailed in Supplementary Table 1. This study involved a total of 883 subjects across 15 studies that assessed serum liver enzymes (ALT and AST). Of these subjects, 801 were diagnosed with NAFLD, while the remaining 82

were identified as having hepatic steatosis. Regarding supplementation, four studies (comprising 249 subjects) [23,30–32] implemented C+P supplementation, whereas the other eleven studies (involving 634 subjects) [24,25,33–41] utilized C supplementation alone. The supplementation protocols across all included studies lasted either 8 or 12 weeks. A risk of bias analysis indicated that all studies were of medium to high quality, as detailed in Supplementary Table 2.

General effects on liver enzymes

We found that curcumin did not alter serum ALT content (SMD: -0.132; 95% CI: -0.636 to 0.372; I^2= 92%, p = 0.607, n = 15 studies, Figure 2A). However, it was able to reduce serum AST (-3.547 U L^{-1}; CI: -5.327 to -1.767; I^2= 76%, p < 0.0001; n = 15 studies, Figure 2B). The Egger test showed that there were no funnel plot asymmetries for ALT (Supplementary Figure 1, p = 0.645) nor for AST (Supplementary Figure 2, p = 0.772). The sensitivity analysis revealed that the study by Jazayeri-Tehrani et al.[36] was influencing the results, indeed when leaving this study out of the model there was a significant reduction in ALT levels (SMD: -0.380; 95% CI: -0.687 to -0.073; I^2= 78%, p = 0.015). Regarding AST, the sensitivity analysis showed that the study by Panahi et al.[24] was altering the results but when this study was excluded for the analysis, the overall effect was similar (-2.844 U L^{-1}; 95% CI: -4.456 to -1.232; I^2= 67%; p = 0.002).

We next introduced in the model several moderators to study the high heterogeneity observed between studies. For that purpose, we performed a meta-regression with relative curcumin daily dose (mg/kg/day) and the intervention length (weeks). Table 1 shows that these moderators did not explain the amount of between-study heterogeneity observed in ALT outcome. For AST, however, there was a reduction to a moderate between-study heterogeneity (I^2 = 50%). The test of moderators showed a tendency (Table 1, p = 0.09) with a likely relationship between the daily relative dose and AST levels. Bubble plots of

these meta-regressions are shown in figure 3. Notably, basal serum levels of AST and ALT do not seem to be a source of heterogeneity under the present model (data not shown).

Following these analyses, we proceeded to examine whether the relationship between curcumin dosage and its effects on serum ALT and AST levels might be non-linear. If so, our aim was to establish a breakpoint in the dose-response curve, which would indicate a dosage at which the beneficial effects of curcumin are reversed. In this regard, no non-linear effects for ALT were observed (Supplementary Figure 3, p = 0.490). However, in the segmented regression analysis presented in Supplementary Figure 4, a significant breakpoint was detected at a dose of 1.135 mg/kg/day (SD = 0.039). Prior to this breakpoint, the analysis indicates a marked decrease in serum ALT levels in response to increasing doses of curcumin (Estimate = -20.358, SD = 4.889, t = -4.164, p = 0.00243). Post-breakpoint, the slope turns positive (Estimate = 20.404, SD = 4.889), indicative of a leveling off in the effect of curcumin on ALT levels. These results are statistically significant at the 0.01 level, reinforcing the hypothesis of a non-linear relationship between curcumin dosage and ALT response. Nevertheless, it is important to acknowledge that the identified breakpoint relies substantially on data from the study by Jazayeri-Tehrani et al.,[36]. Exclusion of this study from the analysis results in the non-linear regression becoming non-significant (Supplementary Figure 5, p = 0.472), with no definitive breakpoints ascertainable.

Furthermore, no non-linear effects for AST were observed (Supplementary Figure 6, p = 0.181). However, in the segmented regression analysis presented in Supplementary Figure 7, a significant breakpoint was detected at a curcumin dose of 2.931 mg/kg/day (SD = 26.302). Prior to this breakpoint, the analysis indicates no significant changes in AST levels in response to increasing doses of curcumin (Estimate = -1.422, SD = 22.383,

t = -0.064, p = 0.951). Post-breakpoint, although there is an increase in the coefficient for the linear term (Estimate = 1.578, SD = 21.736, t = 0.073), it is not statistically significant (p > 0.05). These results suggest that there is no clear evidence of a non-linear relationship between curcumin dosage and AST response, as none of the coefficients for the linear terms or the breakpoint were statistically significant.

Effects of C+P and C on liver enzymes

In figure 1A we show that adding piperine to curcumin is similar to have only curcumin (p = 0.861) for serum ALT levels. We also found a slight tendency towards a difference between C and C+P on AST (p = 0.15, Figure 1B). In fact, while C was able to reduce AST levels (-4.35 U L^{-1}; CI: -6.57 to -2.127, p = 0.0001) this was not the case for C+P (-1.050 U L^{-1}; CI: -5.000 to 2.902; p = 0.602).

As piperine can increase curcumin availability [20], the inclusion of the studies adding piperine to curcumin may also be a source of heterogeneity in the meta-regression shown in Table 1 and Figure 3. Therefore, we next performed the moderators test (length and relative dose) using only C studies. For ALT, the heterogeneity was still high (I^2= 91%) but the test was significant (p= 0.032, Table 2) with a negative relationship between the intervention length and the decrease in ALT levels (see also figures 4A and 4B). For AST, the heterogeneity falls to 13%, and the test was significant (p = 0.002, Table 2) with a negative relationship between the dose and the decrease in AST (Figure 4C). Moreover, there was a similar trend for the relationship between the intervention length and AST decrease (Figure 4D).

DISCUSSION

The meta-analyses presented herein show high (I^2 > 75%) and significant heterogeneity across RCTs examining the impact of curcumin on serum ALT and AST levels in

individuals with NAFLD. We used subgroup analysis in combination with meta-regressions to study the sources of heterogeneity. The subgroup analysis revealed that the combination of curcumin and piperine does not confer benefits on serum aminotransferase levels in NAFLD patients. Meta-regressions with length and dose (mg/kg/d) as *a priori* chosen moderators suggest that these factors are potential sources of heterogeneity. Indeed, our findings indicate a negative correlation between the duration of the intervention and the relative dose of curcumin with reductions in serum aminotransferases. Finally, we found that the dose-response relationship might not be linear, and a dose above 3mg/kg/d may negatively impact serum liver enzymes in NAFLD.

Comparing curcumin with curcumin + piperine

Following the discovery that piperine enhances the bioavailability of curcumin, its incorporation into RCTs has aimed to intensify the therapeutic effects of curcumin. Nevertheless, our analysis indicates that the combination of C+P does not markedly improve the outcomes of curcumin alone on serum ALT levels in individuals with NAFLD. Furthermore, the data suggests a diminution in curcumin's effectiveness on AST circulating levels when combined with piperine. Specifically, C alone is associated with a decrease in AST levels by 4.3 U/L, in contrast to a reduction of 1.0 U/L when used in conjunction with piperine. However, it is crucial to acknowledge that the findings from this subgroup analysis did not achieve statistical significance ($p = 0.15$), a circumstance that may be attributed to the small number of studies ($n = 4$) that have investigated the C+P combination. A possible explanation for these observations might involve piperine's hepatotoxic potential, although toxicity is projected to occur in humans at doses significantly higher (250 mg/day) than those used for augmenting curcumin absorption[42].

In fact, the dose used for improving curcumin availability in the studies analyzed in the present manuscript (5 mg/day) may be beneficial for NAFLD [43].

Alternatively, one could suggest that enhanced cellular availability of curcumin does not provide benefits to patients with NAFLD. Notably, our model shows a better fit when analysis is limited to curcumin-only studies (Table 2) as opposed to when studies assessing both C and C+P are included (Table 3). This implies that piperine may introduce heterogeneity; in fact, heterogeneity (I^2 statistics) dropped from 75% to 13% when the relative dose and the intervention length were considered as moderators for AST in C-only studies.

The impact of curcumin dosage on serum aminotransferase levels

Our findings indicate a negative relationship between AST reduction and the relative dose of curcumin. In this context, it is crucial to note that curcumin is recognized as a potent antioxidant [44]. Research indicates that curcumin specifically targets liver mitochondria to regulate reactive oxygen species (ROS) production in rabbits with steatohepatitis [45]. In humans, there is a marked increase in Complex I-linked respiration in individuals with NAFLD compared to lean counterparts [46]. As NAFLD advances, there is a significant decrease in mitochondrial respiratory capacity, as observed in subjects with liver steatohepatitis [47]. Additionally, mitochondrial ROS levels mildly escalate from obesity to NAFLD, subsequently surging in steatohepatitis [47]. Our analysis predominantly focuses on subjects with NAFLD, with only 82 of the 835 analyzed subjects having steatosis, where ROS production is not overly aggressive and may function as cellular signaling. In such cases, an increase in the antioxidant dosage might interfere with mitochondrial signaling. Exercise studies have shed light on the consequences of obstructing mitochondrial ROS signaling through antioxidant supplementation. Analogous to the mitochondrial dynamics in NAFLD patients' livers, exercise leads to a mild increase in

mitochondrial ROS production and mitochondrial respiration. Intake of polyphenols at doses from ranging from 12 to 20mg/kg/day has been shown to dampen mitochondrial and cellular adaptations in various tissues [48–50]. Considering the critical role of liver mitochondria in NAFLD [47], suppressing ROS production with elevated doses of curcumin or enhancing cellular availability with piperine might negatively impact the hepatocyte. However, whether the antioxidant and/or other biochemical properties of curcumin underlie the dose-response presented herein needs to be mechanistically addressed.

Using segmental regression, we identified that low doses (up to ~1.1 mg/kg/day and ~3 mg/kg/day) could be useful for reducing serum ALT and AST levels in NAFLD. However, these breakpoints should be considered with caution. For ALT, the study by Jazayeri-Tehrani et al., [36] might introduce some variability into the regression model (see Supplementary Figure 5). Additionally, the wide confidence interval for the AST breakpoint suggests a lack of a clear non-linear relationship between curcumin dose and serum AST levels. Thus, it implies a nearly direct relationship (possibly after a low dose breakpoint) between increasing curcumin doses and serum aminotransferase levels.

Impact of the length of the intervention on serum aminotransferase levels

We also observed that extending the duration of the intervention could adversely affect the regulation of liver enzymes. Consistent with our observations, the antioxidant properties of curcumin become apparent after approximately 8 weeks of supplementation in humans [51]. Our findings suggest that prolonging curcumin supplementation from 8 to 12 weeks may negatively impact aminotransferase regulation, indicating that shorter interventions might be more beneficial for modulating aminotransferases in NAFLD. However, this suggestion has limitations since the RCTs included in our analysis only investigated curcumin interventions for 8 or 12 weeks. The absence of data for periods between 8 and 12 weeks could result in a misleading correlation. Although such a pattern

has been noted in Pearson correlations [52], investigations into both short (i.e., 4-8 weeks) and intermediate (i.e., 10 weeks) durations could provide valuable insights into the effect of curcumin supplementation length on aminotransferases.

Limitations

It should be acknowledged that serum levels of aminotransferase are markers of hepatocyte integrity which may not reflect hepatic function [6]. It is also important to note that our analysis revealed that curcumin may be more effective in reducing AST than ALT. In addition, we found that increasing curcumin dose negatively impact AST but not ALT levels. This different response between both enzymes can be because AST is less specific for liver enzymes [6]. Additionally, the constrained number of studies included in our analysis limits the robustness of our conclusions, as we cannot eliminate the possibility that the observed correlations are coincidental. Finally, it should be also considered that the increased AST levels with increased curcumin dose may not be related with curcumin itself. In fact during its processing, curcumin can be contaminated with heavy metals, such as lead [53].

Clinical applications and future research

Considering the limitations, the main clinical implication of our research is that higher curcumin doses may be less effective for reducing aminotransferase levels in NAFLD than lower doses. Our data suggest that curcumin doses ranging from 1 to 3 mg/kg/day may be more effective in reducing these levels. Furthermore, we found no substantial evidence to support the claim that piperine enhances the effect of curcumin on liver aminotransferases in NAFLD. However, several gaps remain that require further investigation. For instance, RCTs should measure aminotransferase and hepatic function at multiple time points. Assessing these outcomes at low to moderate doses (i.e., 1-10

mg/kg/day) from the early to long-term stages could have significant clinical implications for the treatment of NAFLD. This would help not only to validate our findings but also to investigate the potential mechanisms underlying the effects of curcumin on NAFLD.

CONCLUSION

Our analysis revealed significant heterogeneity across RCTs examining the effects of curcumin on liver aminotransferases in NAFLD. This between-study variability can be linked to the intervention length period and the amount of curcumin administered. Indeed, meta-regressions indicated that higher relative doses of curcumin (mg/kg/day) and prolonged supplementation periods could potentially diminish the positive impact of curcumin supplementation on serum ALT and AST levels. Finally, it appears that adding piperine to curcumin curcumin may not be beneficial for decreasing AST levels.

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CONFLICT OF INTEREST

The authors declared that there are no competing interests.

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DATA AVAILABILITY STATEMENT

Data are available from the corresponding author (rcasuso@uloyola.es) upon request.

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FIGURE CAPTIONS.

Figure 1. Flow chart of the systematic review

Figure 2. Forest plot of the general effects as well as subgroup analysis (C and C + P) on ALT (A) and AST (B).

Figure 3. Meta-regression of the moderators in all the studies.

Figure 4. Meta-regression of the moderators in studies using only curcumin.

Table 1. Length and relative dose do not moderate the response of AST and ALT in studies using both curcumin and curcumin+piperine.

	ALT					AST				
Model	**n**	**SMD (95% CI)**	**T^2**	**I^2**	**p**	**n**	**MD (95% CI)**	**T^2**	**I^2**	**p**
Two covariates	13		1.02	93%	0.232	13		3.9	50%	0.090
Dose (mg/kg/d)	13	-0.059 (-0.179 to 0.062)			0.341	13	0.277 (-0.011 to 0.566)			0.059
Length	13	0.283 (-0.045 to 0.612)			0.091	13	0.212 (-0.584 to 1.021)			0.594

Table 2. Length and relative dose moderate the response of AST and ALT in studies supplementing only curcumin.

	ALT					AST				
Model	**n**	**SMD (95% CI)**	**T^2**	**I^2**	**p**	**n**	**MD (95% CI)**	**T^2**	**I^2**	**p**
Two covariates	10		0.92	91%	0.032	10		0.6	13%	0.002
Dose (mg/kg/d)	10	-0.092 (-0.211 to 0.023)			0.132	10	0.263 (0.072 to 0.454)			0.007
Length	10	0.491 (0.122 to 0.859)			0.009	10	0.600 (-0.002 to 1.203)			0.051

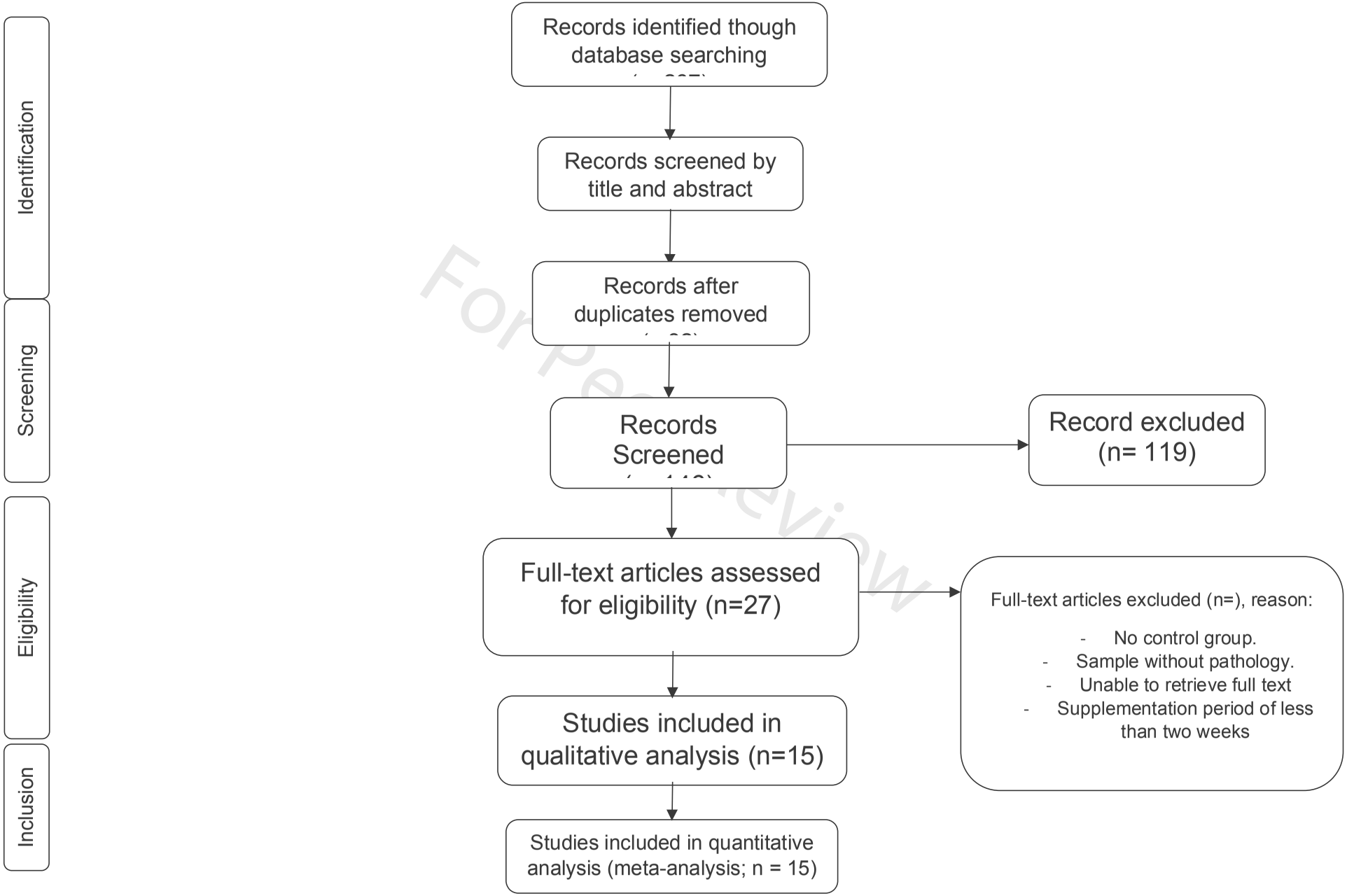

Figure 2

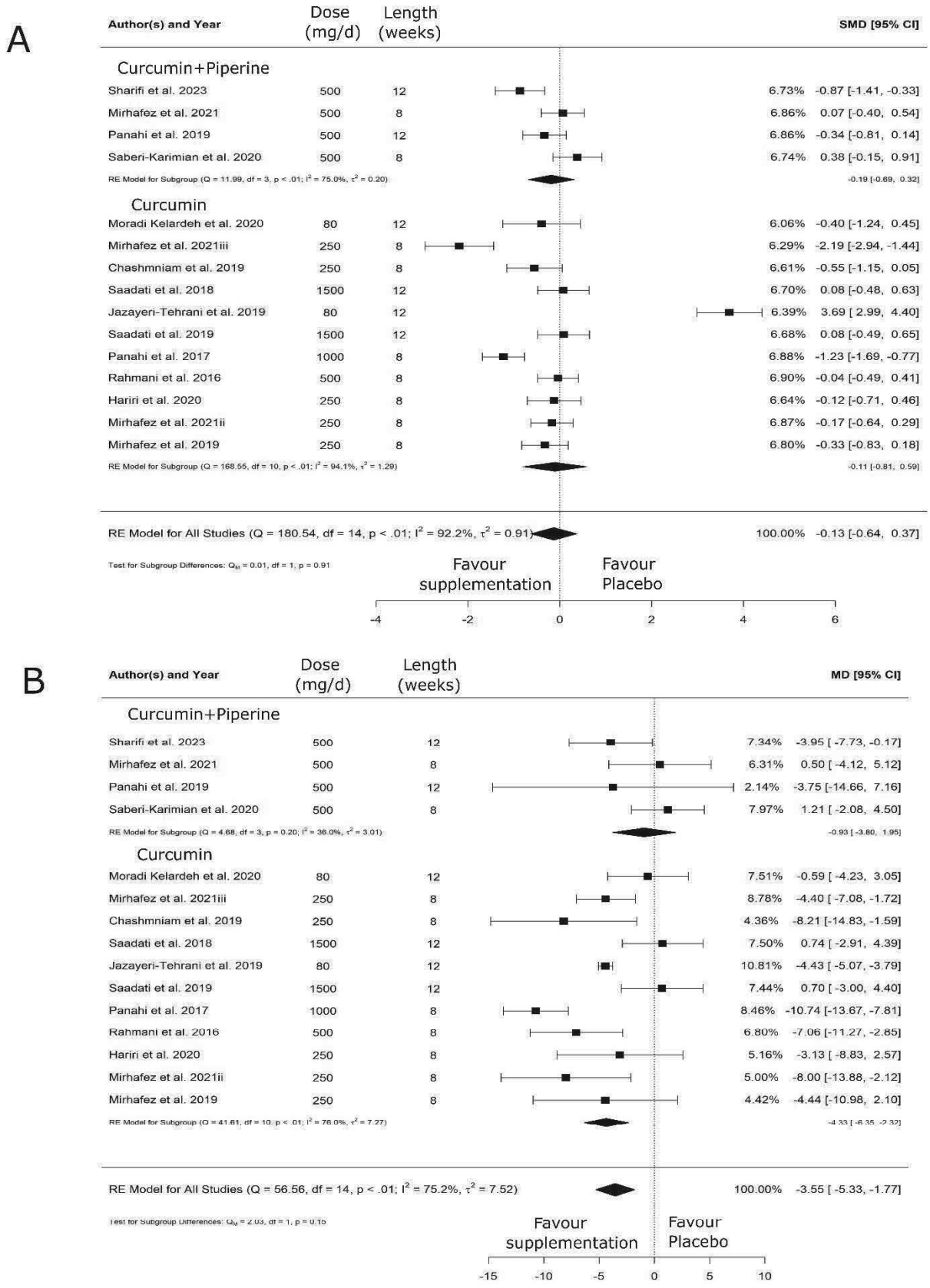
A
Author(s) and Year
Dose (mg/d)
Length (weeks)
SMD [95% CI]
Curcumin+Piperine
Sharifi et al. 2023 500 12 6.73% -0.87 [-1.41, -0.33]
Mirhafez et al. 2021 500 8 6.86% 0.07 [-0.40, 0.54]
Panahi et al. 2019 500 12 6.86% -0.34 [-0.81, 0.14]
Saberi-Karimian et al. 2020 500 8 6.74% 0.38 [-0.15, 0.91]
RE Model for Subgroup (Q = 11.99, df = 3, p < .01; I² = 75.0%, τ² = 0.20) -0.19 [-0.69, 0.32]
Curcumin
Moradi Kelardeh et al. 2020 80 12 6.06% -0.40 [-1.24, 0.45]
Mirhafez et al. 2021iii 250 8 6.29% -2.19 [-2.94, -1.44]
Chashmniam et al. 2019 250 8 6.61% -0.55 [-1.15, 0.05]
Saadati et al. 2018 1500 12 6.70% 0.08 [-0.48, 0.63]
Jazayeri-Tehrani et al. 2019 80 12 6.39% 3.69 [2.99, 4.40]
Saadati et al. 2019 1500 12 6.68% 0.08 [-0.49, 0.65]
Panahi et al. 2017 1000 8 6.88% -1.23 [-1.69, -0.77]
Rahmani et al. 2016 500 8 6.90% -0.04 [-0.49, 0.41]
Hariri et al. 2020 250 8 6.64% -0.12 [-0.71, 0.46]
Mirhafez et al. 2021ii 250 8 6.87% -0.17 [-0.64, 0.29]
Mirhafez et al. 2019 250 8 6.80% -0.33 [-0.83, 0.18]
RE Model for Subgroup (Q = 168.55, df = 10, p < .01; I² = 94.1%, τ² = 1.29) -0.11 [-0.81, 0.59]
RE Model for All Studies (Q = 180.54, df = 14, p < .01; I² = 92.2%, τ² = 0.91) 100.00% -0.13 [-0.64, 0.37]
Test for Subgroup Differences: Q_M = 0.01, df = 1, p = 0.91
Favour supplementation
Favour Placebo
-4 -2 0 2 4 6
B
Author(s) and Year
Dose (mg/d)
Length (weeks)
MD [95% CI]
Curcumin+Piperine
Sharifi et al. 2023 500 12 7.34% -3.95 [-7.73, -0.17]
Mirhafez et al. 2021 500 8 6.31% 0.50 [-4.12, 5.12]
Panahi et al. 2019 500 12 2.14% -3.75 [-14.66, 7.16]
Saberi-Karimian et al. 2020 500 8 7.97% 1.21 [-2.08, 4.50]
RE Model for Subgroup (Q = 4.68, df = 3, p = 0.20; I² = 36.0%, τ² = 3.01) -0.93 [-3.80, 1.95]
Curcumin
Moradi Kelardeh et al. 2020 80 12 7.51% -0.59 [-4.23, 3.05]
Mirhafez et al. 2021iii 250 8 8.78% -4.40 [-7.08, -1.72]
Chashmniam et al. 2019 250 8 4.36% -8.21 [-14.83, -1.59]
Saadati et al. 2018 1500 12 7.50% 0.74 [-2.91, 4.39]
Jazayeri-Tehrani et al. 2019 80 12 10.81% -4.43 [-5.07, -3.79]
Saadati et al. 2019 1500 12 7.44% 0.70 [-3.00, 4.40]
Panahi et al. 2017 1000 8 8.46% -10.74 [-13.67, -7.81]
Rahmani et al. 2016 500 8 6.80% -7.06 [-11.27, -2.85]
Hariri et al. 2020 250 8 5.16% -3.13 [-8.83, 2.57]
Mirhafez et al. 2021ii 250 8 5.00% -8.00 [-13.88, -2.12]
Mirhafez et al. 2019 250 8 4.42% -4.44 [-10.98, 2.10]
RE Model for Subgroup (Q = 41.61, df = 10, p < .01; I² = 76.0%, τ² = 7.27) -4.33 [-6.35, -2.32]
RE Model for All Studies (Q = 56.56, df = 14, p < .01; I² = 75.2%, τ² = 7.52) 100.00% -3.55 [-5.33, -1.77]
Test for Subgroup Differences: Q_M = 2.03, df = 1, p = 0.15
Favour supplementation
Favour Placebo
-15 -10 -5 0 5 10

Figure 3

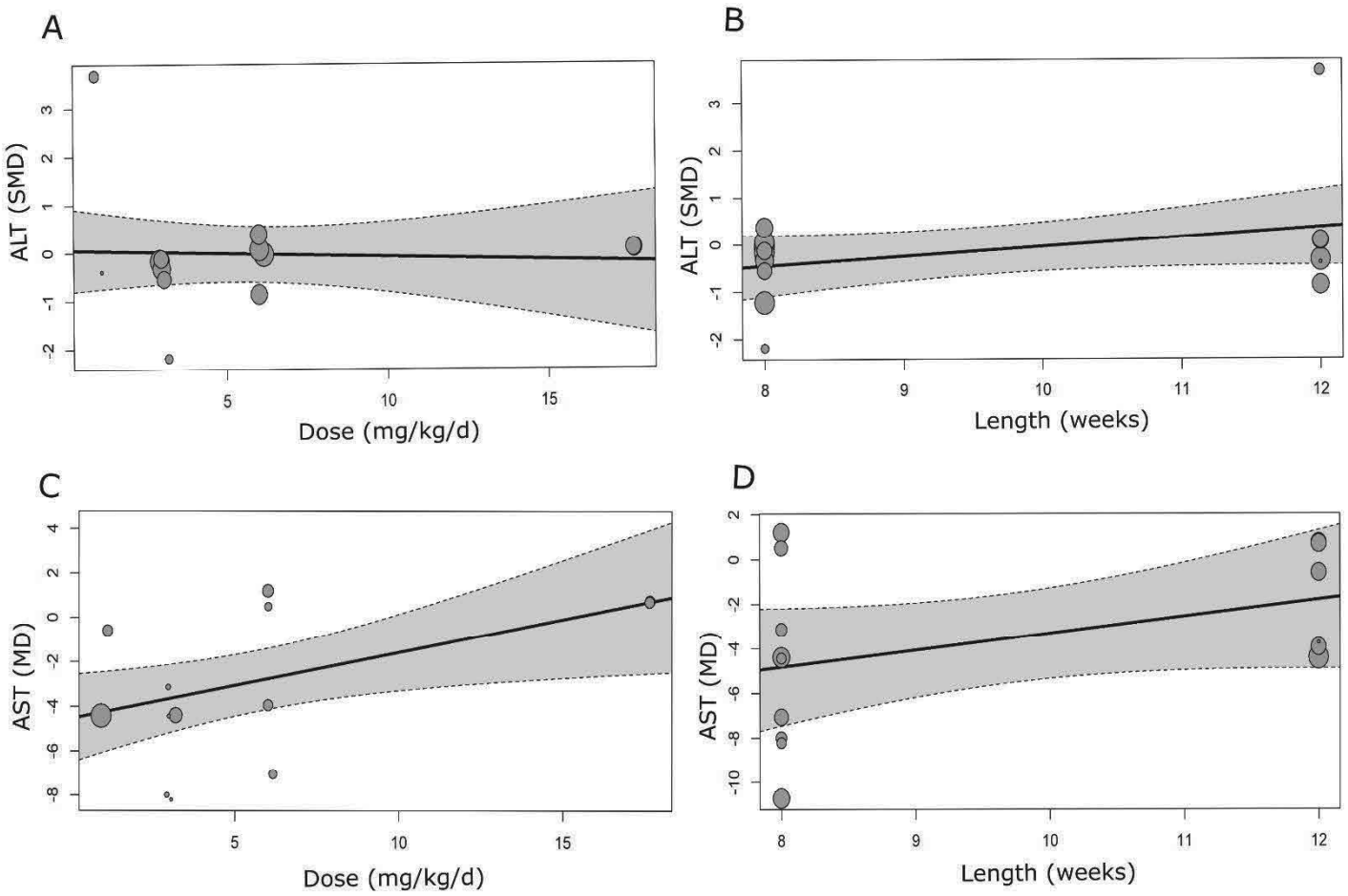
A
ALT (SMD)
Dose (mg/kg/d)
B
ALT (SMD)
Length (weeks)
C
AST (MD)
Dose (mg/kg/d)
D
AST (MD)
Length (weeks)

Figure 4