Efficacy and safety of turmeric extracts for the treatment of knee osteoarthritis: A systematic review and meta-analysis of randomised controlled trials

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Abstract

Purpose of the Review: Finding appropriate pharmacological options to treat osteoarthritis (OA) remains challenging. We aimed to determine the efficacy and safety of all types of turmeric extracts for the management of knee OA.

Recent Findings: Sixteen RCTs of up to 16 weeks duration including 1810 adults with knee OA were included. Eleven RCTs compared the efficacy of turmeric extracts with placebo and five with active comparators (NSAIDs). The overall risk bias of included RCTs was moderate. Turmeric extracts significantly reduced knee pain (SMD -0.82, 95% CI -1.17 to -0.47, I^2=86.23%) and improved physical function (SMD -0.75, 95% CI -1.18 to -0.33, I^2=90.05%) compared to placebo, but had similar effects compared to NSAIDs. BMI was the major contributor to heterogeneity in the placebo-controlled studies (explained 37.68% and 67.24% respectively in the models) and modified the effects of the turmeric on pain and physical function with less improvement with higher BMI (SMD 0.26 95%CI 0.04 to 0.48; SMD 0.48 95%CI 0.21 to 0.74). No significant between group differences were reported for either biochemical markers or imaging outcomes. Turmeric extracts had 12% fewer adverse events than NSAIDs and similar rates to placebo.

Summary: Turmeric extract is a safe and effective option for the symptomatic management of knee OA, compared to placebo or NSAIDs. However, current evidence from short-term studies is heterogeneous and has moderate risk-of-bias leading to some uncertainty about the true effect.

Keywords: Turmeric, curcumin, osteoarthritis, meta-analysis, RCT

Introduction:

Osteoarthritis (OA) is a common chronic disease which mainly affects the knee joints and causes joint pain and function loss [1]. Knee OA imparts a high societal cost with few and suboptimal management options [2]. With no approved disease-modifying drugs available for knee OA, current pharmacological treatment options are limited to analgesics, intra-articular corticosteroids, and non-steroid anti-inflammatory drugs (NSAIDs) [3]. While these medications have only a mild-to-moderate effect size for pain relief, they are associated with gastrointestinal, renal, and cardiovascular complications and are often contraindicated in patients with comorbidities [4]. Consequently, the global demand for a safe and effective therapeutic option for OA have refocused the interest from conventional drugs to complementary and alternative medicines [5]. In particular, one of the potential treatment options for knee OA is turmeric [6].

Turmeric is a generic name for the yellow powder of the rhizome of genus *Curcuma*, including *C. longa* and *C. domestica* [7]. Turmeric has been widely used as a homology of food and medicine in several countries [8]. Curcuminoids (polyphenolic compounds) and polysaccharides are the key components of turmeric [9-11]. Moreover, curcumin is the most active constituent of turmeric and is classified "generally recognised as safe" by the US FDA [8, 12, 13]. The in-vitro, pre-clinical, and translational studies have demonstrated the potential of curcumin, turmeric extracts, and other multi-herbal formulations of curcumin in slowing OA progression and relieving OA-related pain [14, 15]. Previous systematic reviews synthesising the evidence on efficacy and safety of turmeric for the treatment of knee OA are limited by failing to consider the different types of turmeric extracts (holistic, bio-enhanced, curcuminoid-rich, polysaccharide-rich, etc.) and including non-curcuminoid turmeric extracts as thought they were curcumin [15, 16].

Hence, the aim of this systematic review was to assess the efficacy and safety of all types of turmeric extracts, including curcuminoids and non-curcuminoid polysaccharide-rich extracts compared to placebo or active comparator in patients with knee OA.

Methods

We performed this systematic review and meta-analysis according to our pre-published protocol explicitly defining the Population, Intervention, Comparator, Outcome, and Study design (PICOS) of interest for inclusion [17]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria reporting for our systematic review [18].

Search strategy

We searched the online databases PubMed, Scopus, Embase, Web of Science, Cochrane Central Register of Controlled Trial, Google Scholar from inception to May 2020, using keywords: "osteoarthritis and its synonyms" for the population of interest; "curcumin", "turmeric", "curcuminoid", "curcuma", "jiang huang", and "turmerosaccharide" for the intervention of interest; placebo or other active comparator such as NSAIDs for the comparator; pain, physical function, synovitis or cartilage, biochemical markers, rescue medication or discontinuation, and adverse events (AEs) for the outcome of interest; "randomized controlled trial and its synonyms" for study design of interest. We confined the search results to human studies reported in English or Chinese. In addition, the abstract booklet from major conference proceedings and poster sessions were hand-searched for upcoming trials in 2019-2020 in major conferences (European League Against Rheumatism (EULAR), Osteoarthritis Research Society International (OARSI), American Academy of Orthopaedic Surgeons (AAOS), and American College of Rheumatology (ACR)). Clinical trial registry (ClinicalTrials.gov) was also queried to search and identify any upcoming/unpublished trial of interest.

Study inclusion/exclusion criteria

We included all studies based on pre-specified PICOS items described in the protocol [17]. Briefly, we included RCTs of human participants with a clinical diagnosis of knee OA that compared the efficacy and/or safety of turmeric extracts with placebo or active comparators (e.g. NSAIDs). RCTs reporting at least one of the outcomes of interest were included. Non-randomised trials and trials of multi-herbal formulations that contain turmeric and non-*Curcuma* species extracts were excluded. Studies comparing combinations were included only if the same active intervention (except turmeric) was also present in the comparator group (e.g. both the treatment and control group received diclofenac) [19].

Study selection was performed by two reviewers (Z.W.&A.S.) independently. Any disagreements in inclusion were resolved through consensus and/or consultation with senior authors (B.A.).

Data collection, risk of bias, and quality assessment

Two reviewers (Z.W.&A.S.) independently extracted data from the included studies and discrepancies in data consistency were resolved through discussion between the reviewers. We extracted details of study design, characteristics of the population [age, sex, and body mass index (BMI)], sample size, intervention details and dosage, duration of follow-up, type of comparator placebo/active comparator, mean change values for efficacy outcome measures with standard deviation (SD), number of AEs reported, and change in pain medication. We included intention-to-treat data in our analysis, whenever available.

For each outcome, when available, we used the change from baseline to the longest reported follow-up. When mean change was not reported, we calculated the arithmetic difference between baseline and follow-up. Where trials reported pain measured by more than one, we selected the pain measure to use in the following order of priority: Visual Analog Scale (VAS) for pain during any activity; the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); the pain subscale of the Knee injury and Osteoarthritis Outcome Score (KOOS); and any other reported pain measures.

The physical function subscale of WOMAC was the preferred measure for the assessment of functional improvement. In the absence of the WOMAC function subscale, other functional measurements or WOMAC total scores were used (17 subscales for function out of 24 subscales in the total WOMAC). The number of participants who experienced any AE and who commenced or discontinued any pain medication (rescue medication and/or any analgesics) were extracted, when available. For studies with incomplete data or unavailable data, we requested that the corresponding authors of the primary studies provide missing or additional data. In the event of no response from the authors of the primary studies, and unpublished original trial for which data were not available, outcomes were extracted from previous systematic reviews that included the missing data from the primary trial where available.

Standard deviations (SD) were also extracted if reported, otherwise, SD were calculated by using the following methods: 1) standard error or confidence intervals; 2) SD for change scores (SD_{diff}) were imputed using the SD from baseline (SD_{bl}) to SD from post-intervention (SD_{pi}) (Supplementary Formula-1, the conservative value of r=0.5 was used [20]); 3) *P* values that relate to the differences between mean changes in two groups according to the Cochrane handbook 5.1 Section 7.7.3. [21].

For studies with more than two arms [22-26], we split the shared arm into two groups and analysed it with the independent comparator arms to enable comparison [21]. For example, trials comparing high-dose and low-dose curcumin, were divided into a corresponding number of pairwise comparisons of the study versus the placebo group with the number of the placebo group halved [26]. On some occasions, pain or WOMAC physical function changes were inferred from graphical information in the published papers [27], with missing SD imputed from other trials with the same outcome assessment tool [28].

The methodological quality of the included RCTs was assessed using the Cochrane risk-of-bias (RoB) tool [29] by two reviewers (Z.W.&A.S.) independently using Review Manager (RevMan) 5.4.1 (The Cochrane Collaboration, 2020) [30]. A total of seven domains were evaluated following the Cochrane Handbook V.5.1.0, Chapter 8.5: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Any disagreements in the evaluation were resolved through discussion with the adjudicator (B.A.).

Data synthesis and statistical analysis

Due to variation in outcome measures, the standardised mean difference (SMD) for the mean change from baseline to follow-up scores between groups were calculated using Hedges' g effect sizes. We used the risk difference (RD) to analyse and pool categorical outcomes, including AEs and rescue medications. We assessed the clinical heterogeneity based on PICOS characteristics of the included RCTs. Statistical heterogeneity was assessed by I^2 statistic (I^2 >50% was considered substantial heterogeneity) [31]. We used a random-effects model with restricted maximum-likelihood to meta-analyse the effect estimates. Publication bias was assessed visually with funnel plots [32], and the trim-and-fill method was used to estimate the effect of publication bias (if any) [33].

Separate comparisons were conducted based on comparator types, such as studies comparing turmeric extract with placebo or NSAIDs (ibuprofen and diclofenac). To further explore the potential heterogeneity among the trials with placebo as a comparator, we performed a *post hoc* meta-regression of the effect sizes (SMDs) on study-level covariates: baseline characteristics of participants (age, gender, BMI), dosage, and duration; subgroup analyses were conducted to compare different formulation types (with or without bio-enhanced), type of pain measures (VAS vs. WOMAC/KOOS), RoB, trial location (Asian or not), and types of funding (investigator-initiated or industry). The association between covariate and effect sizes was analysed, and the proportion of heterogeneity that covariate explained (measured using residual I^2 statistics) and effect modification were reported [34, 35]. The statistical analyses were performed using STATA version 16 (STATA Corp., Texas, USA) and RevMan. We used a narrative synthesis approach to present the results of outcomes where data were not available/suitable for meta-analysis (biochemical markers and imaging biomarkers).

Results

A total of 130 citations were identified following the initial database search and exclusion of the duplicates. A total of 99 citations were excluded after screening based on title and abstract, and 31 full-text articles were assessed for eligibility. Overall, 16 RCTs qualified prespecified inclusion criteria as described in the protocolwere included in this systematic review (Figure-1).

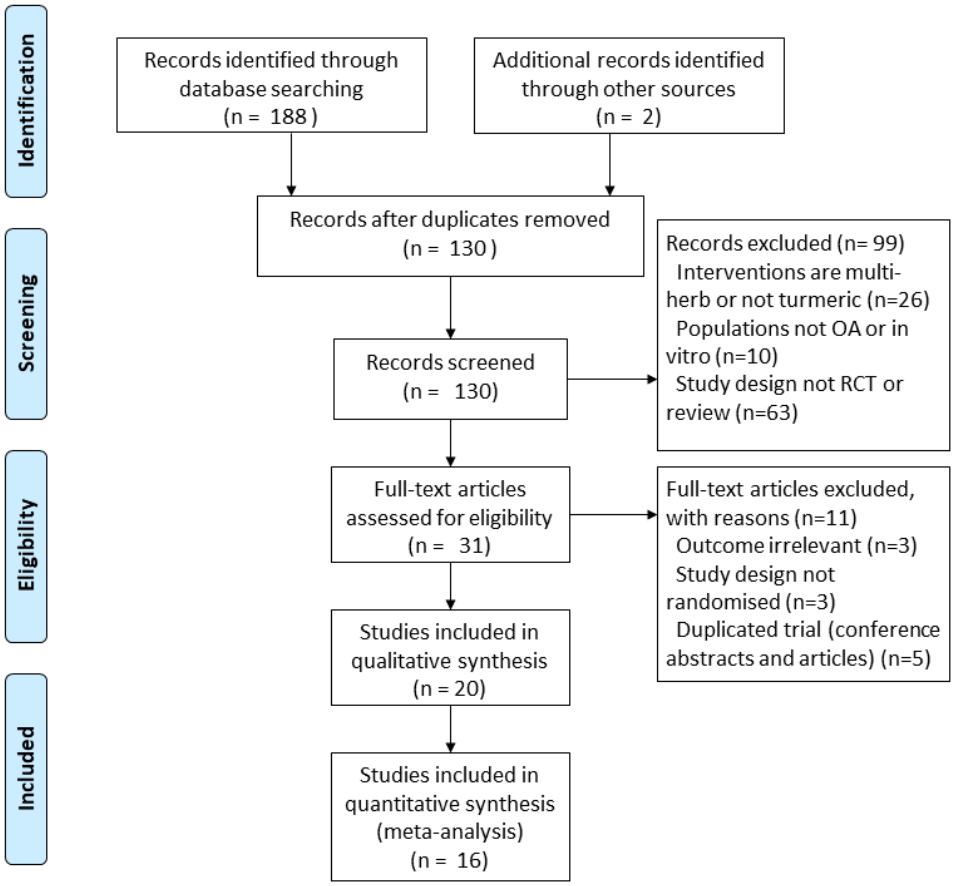

Figure. 1 PRISMA diagram of study selection, inclusion and exclusion of studies

Characteristics of the included studies

Sixteen RCTs with a total of 1810 participants were included. Eleven studies compared turmeric extract formulations with placebo [15, 19, 22, 26, 36-42], with two studies using diclofenac in both treatment and comparator arms.[19, 38] Five studies were a head-to-head comparison between turmeric extract and NSAIDs (either ibuprofen or diclofenac) [23, 27, 43-45] (Table-1 and Supplementary Table-1).

The studies were conducted between 2009 and 2020. The majority were conducted in Asia (five from India [22, 23, 27, 38, 40], three each from Thailand [19, 43, 45] and Iran [15, 37, 41], one each from Japan [36], Indonesia [44], and Armenia [39]), while one study each was conducted in Belgium [26] and Australia [42]. The largest trial consisted of 367 primary knee osteoarthritis patients from Thailand [45].

Twelve studies assessed pain using VAS [15, 19, 22, 23, 26, 27, 36-38, 40, 42, 44], ten reported WOMAC scale [15, 22, 27, 37-42, 45], and seven studies reported both VAS and WOMAC [15, 22, 27, 37, 38, 40, 42]. Few studies used localised versions of WOMAC, such as Japanese [36] and Indian versions [22] of the WOMAC scale adapted to the local lifestyle. The daily dose of different formulations of turmeric extract varied across studies from 80 mg to 2000 mg. Included RCTs used turmeric extract formulations with varying bioavailability enhancers that were bio-optimised to polysaccharides [22], turmeric oil [23], liposome [27], and BioPerine® (piperine standardised minimum to 95%) [37]. Ten of the included RCTs were registered in a clinical trials registry [22, 23, 26, 27, 38-42, 45], and 37.5% of included RCTs were investigator-initiated, 37.5% were industry-funded trials and 25% did not report any funding details.

Assessment of quality and risk of bias

The overall risk of bias of included trials was moderate with five trials assessed being high quality [23, 26, 39, 40, 42], according to the Cochrane RoB tool (Supplementary Figure-1). Nine of the included RCTs were assessed as having a high risk for incomplete outcome data reporting either due to loss to follow-up or to not employing intention-to-treat (ITT) analysis [15, 19, 27, 36, 37, 41, 43-45].

Table 1. Characteristics of trials included in the analysis by year of publication.

Trial No.	Author, Year, and Country	Group	No. of Patients	Women, No. (%)	Age, y [*]	BMI [*, †]	Weeks	Rescue medication	Registered	Funding
1	Kuptniratsaikul et al, 2009, Thailand [43]	T	55	41 (78.8)	61.4 (8.7)	26.4 (3.7)	6	None	-	Investigator -initiated
		I	52	45 (81.8)	60.0 (8.4)	26.8 (4.8)				
2	Moharamzad et al, 2011, Iran (Unpublished) [15]	T	35	-	-	-	10	-	-	-
		P	32	-	-	-				
3	Kertia et al, 2012 Indonesiana [44, 48]	T	39	24 (61.5)	64.1 (8.8)	26.3 (3.6)	4	Paracetamol	-	Investigator -initiated
		D	41	29 (70.7)	64.56 (8.9)	26.4 (4.8)				
4	Pinsornsak et al, 2012 Thailand [19]	T	44	62 (83.0)	>44.0	-	12	None	-	-
		P	44			-				
5	Madhu et al, 2013 India [22]	T_a	30	17 (56.7)	56.6 (10.6)	27.0 (4.6)	6	Paracetamol	yes	-
		P_a	30	17 (56.7)	56.8 (10.0)	28.0 (4.2)				
		T_b	30	24 (80.0)	58.2 (9.3)	27.9 (5.2)				
		P_b	30	25 (83.3)	56.8 (8.0)	27.8 (3.1)				
6	Kuptniratsaikul et al, 2014 Thailand [45]	T	185	139 (86.9)	60.9 (6.9)	26.6 (4.0)	4	Tramadol	yes	Investigator -initiated
		I	182	157 (91.8)	60.3 (6.8)	26.5 (3.7)				
7	Nakagawa et al, 2014 Japan [36]	T	25	14 (77.8)	71.9 (5.3)	25.1 (2.7)	8	Celecoxib / pain relief patches	-	Industry
		P	25	18 (78.3)	66.1 (7.2)	24.8 (2.3)				
8	Panahi et al, 2014 [‡] & Panahi et al, 2015 [‡] Iran [37, 47]	T	27	22 (73.7)	57.3 (8.8)	28.8 (3.2)	6	Naproxen	-	Investigator -initiated
		P	26	22 (81)	57.6 (9.1)	29.6 (4.5)				
	Rahimnia et al, 2015 [‡] Iran [48]	T	19	14 (73.7)	57.3 (8.8)	28.8 (3.2)	6			
		P	21	17 (81.0)	57.6 (9.1)	29.6 (4.5)				
9	Srivastava et al, 2016 India [38]	T	78	53 (67.9)	50.2 (8.1)	28.3 (5.1)	16	Diclofenac	yes	Industry
		P	82	50 (61.0)	50.3 (8.6)	27.4 (5.8)				
10	Haroyan et al, 2018 Armenia [39]	T	66	60 (90.9)	54.7 (8.8)	28.3 (3.6)	12	None	yes	Industry
		P	68	65 (96.6)	56.0 (8.6)	28.8 (3.4)				
11	Panda et al, 2018 India [40]	T	25	-	55.2 (8.6)	25.4 (2.8)	8	Paracetamol	yes	Industry
		P	25	-	53.1 (8.3)	25.0 (1.9)				
12	Gupte et al, 2019 India [27]	T	17	11 (64.7)	57.0 (7.5)	28.2 (5.8)	12	None	yes	Industry

Trial No.	Author, Year, and Country	Group	No. of Patients	Women, No. (%)	Age, y [*]	BMI [*, †]	Weeks	Rescue medication	Registered	Funding
		I	25	23 (92.0)	54.0 (8.0)	30.5 (5.1)				
13	Henrotin et al, 2019 Belgium [26]	T_a	49	39 (79.6)	60.9 (9.8)	29.4 (4.9)	12	Paracetamol	yes	Industry
		T_b	47	40 (85.1)	61.4 (7.5)	30.4 (5.2)				
		P	45	34 (75.6)	63.3 (7.7)	29.4 (5.2)				
14	Shep et al, 2019 India [23-25]	T_a	71	21 (29.6)	52.6 (4.5)	-	4	Paracetamol	yes	-
		T_b	70	25 (35.7)	53.1 (4.2)	-				
		D	69	21 (30.4)	52.1 (3.8)	-				
15	Hashemzadeh et al, 2020 Iran [41]	T	36	29 (80.6)	54.1 (5.8)	-	6	Paracetamol	yes	Investigator -initiated
		P	35	31 (88.6)	56.5 (5.8)	-				
16	Wang et al, 2020 Australia [42]	T	36	18 (50.0)	61.3 (8.5)	29.9 (6.3)	12	Paracetamol	yes	Investigator -initiated
		P	34	21 (62)	62.4 (8.8)	30.6 (7.2)				

Abbreviations: T, Turmeric; P, Placebo; I, Iburprfen; D, Diclofenac; BMI, Body Mass Index.

[*] Data expressed as mean (SD) or otherwise specified.
[†] Calculated as weight in kilograms divided by height in meters squared.
[‡] The Panahi et al. 2014 & 2015 and Rahimnia et al, 2015 reported results from the same trial conducted at Baqiyatallah University of Medical Sciences, Tehran, Iran.

Effect on knee pain

Twelve RCTs included 577 and 494 participants in the turmeric extract and placebo groups, respectively [15, 19, 22, 24, 26, 36-42], and five RCTs included 342 and 306 participants in the turmeric extract and active control (NSAIDs) group [23, 27, 43-45]. Turmeric extract had a large effect on knee pain (SMD = -0.82, 95%CI -1.17 to -0.47) compared to placebo but a similar effect to NSAIDs (SMD = -0.09, 95%CI -0.30 to 0.12) (Figure-2). Substantial heterogeneity was observed in the turmeric vs. placebo comparison (I^2=86.23%), and moderate heterogeneity in the turmeric vs. NSAIDS group (I^2=34.97%).

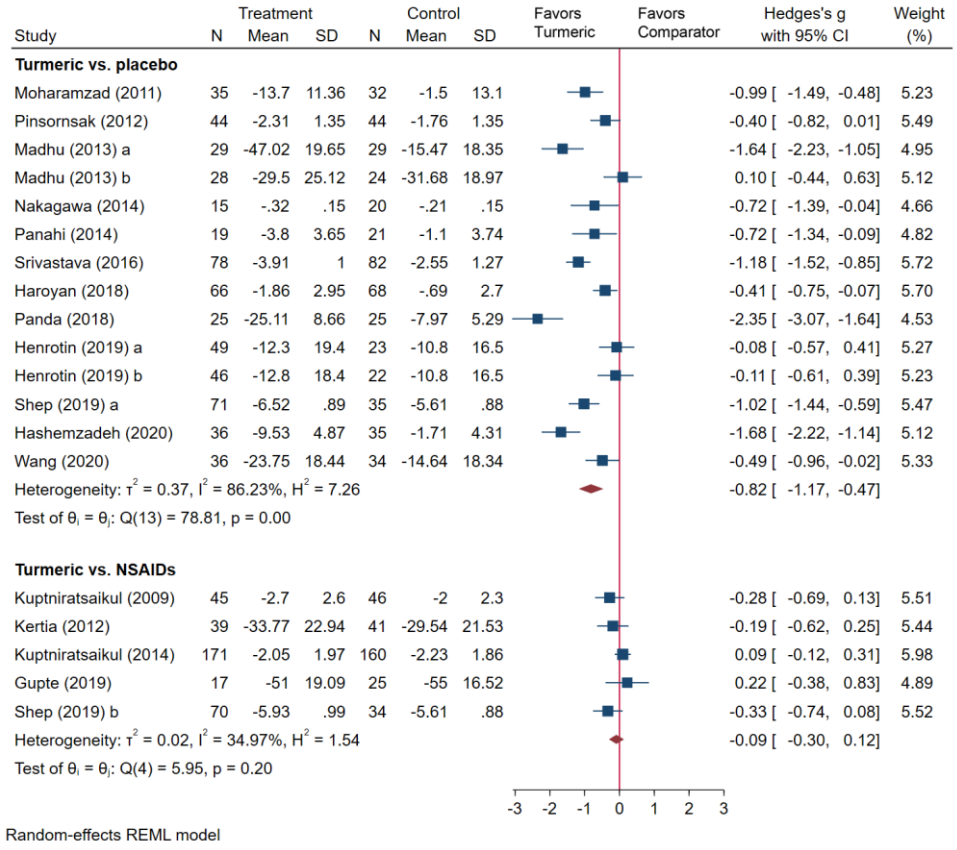

Figure. 2 Forest plot depicting the standardised mean difference of change in knee pain

Physical function

Ten RCTs included 508 and 465 participants in the turmeric extract and placebo groups, respectively [15, 22, 25, 26, 37-42], and three RCTs included 258 and 219 participants in the turmeric extract and active control (NSAIDs) group [23, 27, 45]. Compared to placebo, turmeric had a clinically and

statistically significant effect on improving knee function (SMD=-0.75, 95%CI -1.18 to -0.33), whereas there was no difference compared to NSAIDs (SMD=-0.14, 95%CI -0.36 to 0.09) (Figure-3). Substantial heterogeneity was observed for physical function in the turmeric vs. placebo (I^2=90.05%) and small heterogeneity in the turmeric vs. NSAIDs (I^2=20.02%).

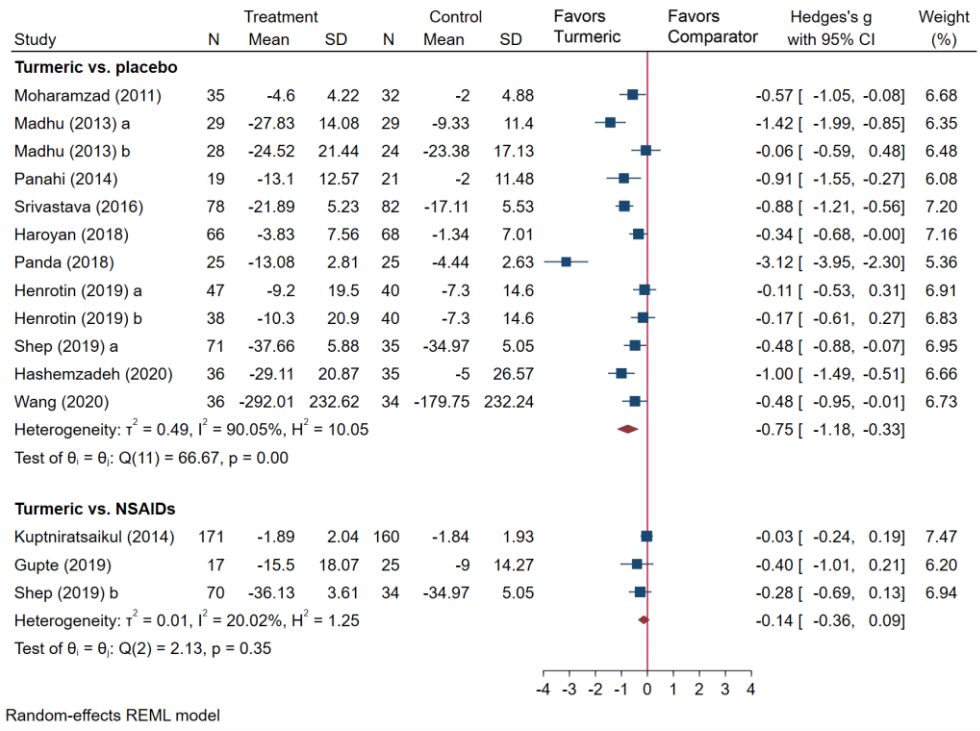

Figure. 3 Forest plot depicting the standardised mean difference of change in knee physical function

Meta-regression and subgroup analysis

We only analysed heterogeneity in the turmeric versus placebo group for pain and physical function by meta-regression or subgroup analysis (Supplementary Table-2). The meta-regression for the primary outcome of pain, with study-level participant BMI as a covariate, showed that 82.77% of the residual variance (heterogeneity) was between-study (while only 17.23% of variance was within-study) and BMI was able to explain 37.68% (adjusted R^2) of the between-study variance for SMDs of pain, with one unit increase in BMI modified 0.26 (0.04 to 0.48) less SMD of turmeric improvement in pain (Supplementary Table 2 and Figure-2 for heterogeneity proportion). Similarly, regression with the study-level participant age demonstrated that 85.67% of the residual variance was between-study and 17.94% (adjusted R^2) of between-study variance was explained by age for SMDs of pain, with one year increase in age modified 0.07 (-0.01 to 0.14) less SMD of turmeric improvement in pain. Meta-

regression analysis for physical function with BMI as a covariate reported that 81.67% of the residual variance was between-study and 67.24% (adjusted R^2) of the between-study variance was explained by BMI. Every unit increase in BMI modified 0.48 (0.21, 0.74) less SMD of turmeric improvement in physical function (Table 2. bubble plots for meta-regression were provided in Supplementary Figures-3~6). There are significant associations between treatment effect for pain and physical function with BMI, patients with less BMI was more likely to respond. Similar but nonsignificant association were observed for effect sizes with age, with older people less likely to respond. Meta-regression for other covariates, such as duration, dosage and study-level gender proportion, did not explain or explained less than 10 % (adjusted R^2) of the variance.

Among trials comparing turmeric and placebo, subgroup analysis suggested that RCTs conducted in Asia tended to report statistically significantly larger effects of both pain and physical function than those conducted in other countries (Supplementary Figure-7). Other study-level characteristics (formulation types, bio-enhancer, RoB, pain measurement tools and funding) did not demonstrate any evidence of effect modification.

Biomarkers

Four studies examined the inflammatory biomarkers (TNF-α, TNF-β, IL-6, and hs-CRP) [27, 38, 39, 48]. Cartilage and synovial markers, including Coll-2 and CTX II, were reported in two trials [26, 27]. Three studies reported malondialdehyde as an anti-oxidant markers [38, 44, 47]. Laboratory or biochemistry parameters for safety were reported in three trials [23, 36, 41]. One study each assessed synovial fluid inflammatory and anti-oxidant biomarkers [44] and reported MRI outcomes of effusion synovitis volume and cartilage composition [42]. No significant between-group differences were reported for any of these biomarkers.

Adverse events

Ten studies with 13 comparisons reported AEs [22-24, 26, 37-40, 42, 43, 45] and 6 studies did not [15, 19, 27, 36, 41, 44]. Eight RCTs included 423 and 368 participants in the turmeric extract and placebo groups respectively [22, 24, 26, 37-40, 42], and three RCTs included 303 and 268 participants in the turmeric extract and active control (NSAIDs) groups respectively [23, 43, 45]. AEs were lower in

turmeric extract groups compared to NSAIDs (RD -12%, 95%CI -24% to -1%), while rates of AE's were similar in groups treated with turmeric extract and placebo (Figure-4). Modest heterogeneity was observed for AEs in both groups.

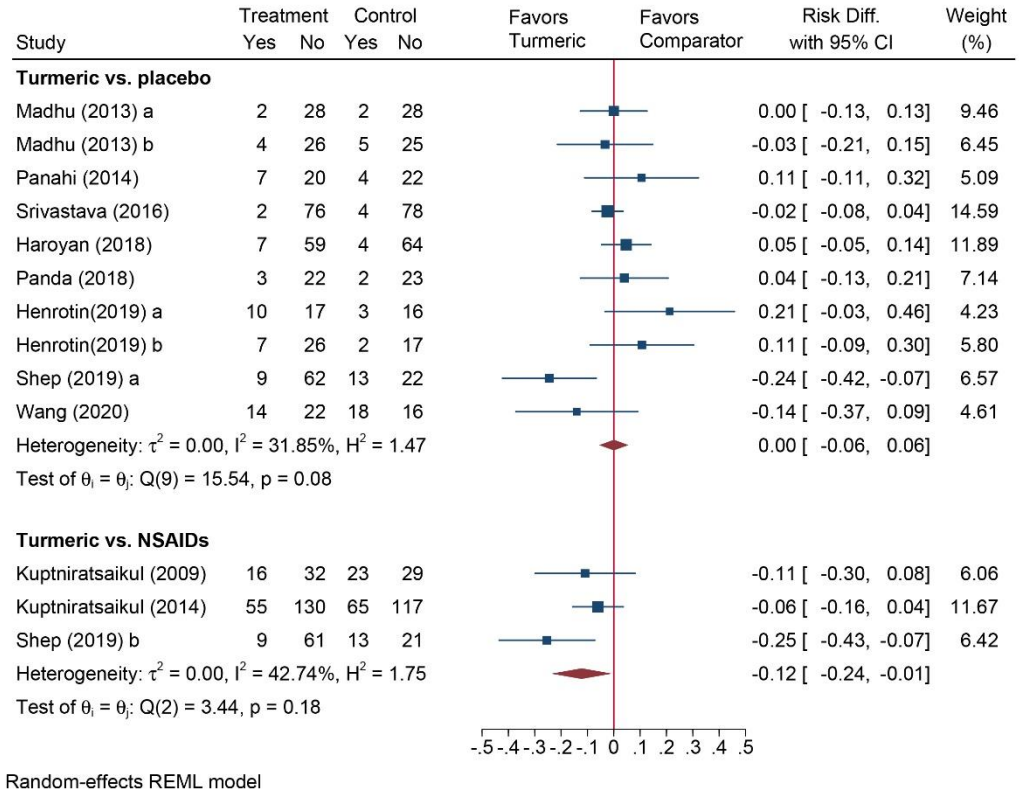

Figure 4 Forest plot of incidence of any adverse events

Rescue medication and medication discontinuation

Six trials reported the use of rescue medications [22, 23, 26, 40, 42, 45]. There was no significant differences in the rate of rescue medication usage between turmeric extract and NSAIDs groups (RD=2%, 95%CI -1% to 4%) or the placebo group (RD=-13%, 95%CI -24% to 1%, Supplementary Figure-8A). Three studies comparing turmeric extracts and placebo reported pain medication discontinuation for both groups [36, 37, 41]. Turmeric groups had a significantly higher rate of cessation of pain medication compared to placebo groups (RD 36%, 95%CI 10% to 61%, Supplementary Figure-8B).

Publication bias

Publication bias may exist in the turmeric vs. placebo or turmeric vs. NSAIDs groups publications (Supplementary Figure-9~11), but this did not change the statistical significance of the estimate by trim-and-fill method.

Discussion

To the best of our knowledge, this is the most comprehensive systematic review and meta-analysis assessing the efficacy and safety of all forms of turmeric extracts for the treatment of knee OA. We found that turmeric improves pain and physical function compared to placebo and showed a comparable effect to NSAIDs. The effect sizes for improvement in pain and physical function compared to placebo were large (SMD greater than 0.75); however, the maximum duration of included studies was only 16 weeks. Rates of AEs were lower for turmeric compared to NSAIDs, and were comparable to placebo. However, heterogeneity was high and largely unexplained by study-level covariates, which lead to some uncertainty about the true effect. The limited evidence available does not suggest that turmeric affected biochemical (inflammatory and cartilage specific) or imaging biomarkers.

Our review included a greater number of studies compared to previous systematic reviews [15, 49], which improved the power of this study to provide a more realistic and precise effect size (SMD=-0.82; 95% CI:-1.17, -0.47 turmeric vs. placebo). In addition, in congruence with our recent study [42], we found that the OA patients taking turmeric were less likely to commence pain rescue medications and more likely to discontinue existing pain medications. Wu et al. included 5 studies (n=599) and suggested that curcumin could significantly improve the WOMAC score (SMD=-0.96; 95% CI:-1.81, -0.10; *P*=0.03) and VAS score of OA patients (SMD=-1.65; 95% CI:-2.11, -1.19) [49]. Bannuru et al.'s meta-analysis (included five studies, n=331 for curcuminoid vs. placebo; two trials, n=422 for curcuminoid vs. NSAIDs) and suggested that curcuminoids were more effective than placebo for pain relief (SMD= -0.81; 95% CI: -1.25, -0.37) and functional improvement (SMD= -0.48; 95% CI: -0.74, -0.22) but showed no statistically significant differences in efficacy outcomes compared to NSAIDs [15]. Onakpoya's review included seven studies (n=797) and reported a large effect size for pain reduction (SMD -3.50 95%CI -4.99 to -2.01) and function improvement (SMD -3.92 95%CI -6.23 to -0.35) compared to comparators including placebo and NSAIDs [16]. A previous systematic review on the

effect of turmeric extracts on chronic inflammatory diseases (included rheumatic diseases) reported no significant between-group differences in inflammatory markers between turmeric extracts and placebo, which is consistent with our results [50].

Most of the current pharmacological therapies have an effect size ranging from 0.18 to 0.44 for pain compared to placebo [51, 52]. Effect sizes for the turmeric extract group from short-term follow-up studies show substantially larger effects in pain reduction and improvement in physical function compared to placebo with an effect size (SMD) of -0.82 and -0.75 respectively. Similarly, there was a smaller effect on improvement in pain and function (SMD of -0.09 & -0.14) when compared to NSAIDs. These results are only from short-term studies (maximum follow-up was 16 weeks) but look promising for a medicine with good safety profile. Most of the current pharmacological therapies in OA typically have poor safety profiles [53], therefore having a therapy that is safe as well as effective is an important advance. Notably, we found that the AEs reported in the turmeric group were similar to the placebo group and 12% less than those reported in the NSAIDs group. However, there may be under-reporting for AEs as six RCTs did not report AEs. This might have contributed to the smaller reduction in AEs (considering the poor safety profile of NSAIDs) comparing to NSAIDs [54].

The meta-analyses displayed substantial heterogeneity, which may be explained by study-level covariates such as BMI, and age. Higher study-level participant BMI was significantly associated with lower turmeric treatment effect sizes for pain and physical function compared to placebo. Negative correlations between study-level participant age and pooled effect sizes of both pain and physical function were reported, which explained modest or smaller amount of between-study heterogeneity. Formulations strategies are considered to enhance the bioavailability of curcuminoids to a higher extent; however, *post-hoc* meta-regression showed no notable association between the SMDs and formulation types.

The key strength of our study was the extensive search to include all forms of turmeric extracts in RCTs, including both placebo-controlled and active-controlled (e.g. NSAIDs). There are few restrictions to be applied while interpreting our results, first the meta-regression analysis was performed *post-hoc*. Second, all of the included studies were of short duration (<=12 weeks), with the exception of one study

with 16 weeks of follow-up, thus our conclusions are only on the short-term efficacy and safety of turmeric extracts for the treatment of knee OA. Third, most of the included trials were from Asian countries with presumably fewer Caucasian participants. Thus, the generalisability of these results might be limited. Fourth, as few studies assessed the biochemical and imaging biomarkers, we could not conduct meta-analyses for these outcomes, the effects on biochemical and imaging changes is unclear. Last, due to the incomplete reporting of data from some trials, SD values were imputed using methods as described in the methods section, meaning there might be slight distortion on the pooled SMDs. However, we conducted a sensitivity analysis by omitting trials with imputed SD values, and the results were similar.

Conclusion

Our meta-analyses from short-term RCTs reported that turmeric extracts caused a large improvement in pain and physical function compared to placebo but similar improvements with a better safety profile than NSAIDs in people with knee OA. The large effect size and good safety profile favouring the turmeric suggests that turmeric extracts are a viable pharmacological treatment option for symptomatic management of knee OA. Long-term safety and efficacy data are lacking; future high-quality RCTs with longer follow-up duration are warranted to assess the long-term safety and efficacy of turmeric extracts.

Authors' contributions

B.A. conceived and designed the study. Acquisition and assessment of data were performed by Z.W. and A.S. Data extraction and analysis were conducted by Z.W., B.A and A.S. Z.W., A.S., and B.A. drafted the manuscript and all authors contributed with a thorough and critical revision for important intellectual content. All authors have approved the final version of this manuscript

Conflicts of Interest

No conflicts of interest to disclose.

Human and Animal Rights.

This article does not contain any studies with human or animal subjects performed by any of the authors.

Reference

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *The Lancet.* 2019;393(10182):1745-1759.
2. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis.* 2014;73(7):1323-1330.
3. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthr Cartil.* 2019;27:1578-1589.
4. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part I: Critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthr Cartil.* 2007;15(9):981-1000.
5. Singh S. From Exotic Spice to Modern Drug? *Cell.* 2007;130(5):765-768.
6. Asher GN, Spelman K. Clinical Utility of Curcumin Extract. *Altern Ther Health Med.* 2013;19(2):20-22.
7. Ayati Z, Ramezani M, Amiri MS, et al. Ethnobotany, Phytochemistry and Traditional Uses of Curcuma spp. and Pharmacological Profile of Two Important Species (*C. longa and C. zedoaria*): A Review. *Curr Pharm Des.* 2019;25(8):871-935.
8. Goel A, Jhurani S, Aggarwal BB. Multi-targeted therapy by curcumin: how spicy is it? *Mol Nutr Food Res.* 2008;52(9):1010-1030.
9. Yue GG, Chan BC, Hon PM, et al. Immunostimulatory activities of polysaccharide extract isolated from Curcuma longa. *Int J Biol Macromol.* 2010;47(3):342-347.
10. Sahebkar A. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. *Phytother Res.* 2014;28(5):633-642.
11. Chandrasekaran CV, Kannan Sundarajan JRE, Gururaja GM, et al. Immune-stimulatory and anti-inflammatory activities of Curcuma longa extract and its polysaccharide fraction. *Pharmacognosy Res.* 2013;5(2):71.
12. Gupta SC, Sung B, Kim JH, et al. Multitargeting by turmeric, the golden spice: From kitchen to clinic. *Mol Nutr Food Res.* 2013;57(9):1510-1528.
13. Prasad S, Gupta SC, Tyagi AK, et al. Curcumin, a component of golden spice: from bedside to bench and back. *Biotechnol Adv.* 2014;32(6):1053-1064.
14. Peddada KV, Peddada KV, Shukla SK, et al. Role of Curcumin in Common Musculoskeletal Disorders: a Review of Current Laboratory, Translational, and Clinical Data. *Orthop Surg.* 2015;7(3):222-231.
15. • Bannuru RR, Osani MC, Al-Eid F, et al. Efficacy of curcumin and Boswellia for knee osteoarthritis: Systematic review and meta-analysis. *Semin Arthritis Rheum.* 2018;48(3):416-429. **This review discussess the evidence of curcuminoid relieving symptoms of knee osteoarthritis.**
16. Onakpoya IJ, Spencer EA, Perera R, et al. Effectiveness of curcuminoids in the treatment of knee osteoarthritis: a systematic review and meta-analysis of randomized clinical trials. *Int J Rheum Dis.* 2017.
17. Wang Z, Singh A, Antony B. Efficacy and safety of turmeric extracts in knee osteoarthritis: protocol for a systematic review and meta-analysis of randomised controlled trials. *medRxiv.* 2020.
18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009; 339:b2700.
19. Pinsornsak P, Niempoog S. The Efficacy of *Curcuma Longa L.* Extract as an Adjuvant Therapy in Primary Knee Osteoarthritis: A Randomized Control Trial. *J Med Assoc Thai* 2012;95:S51-S58.
20. Rongwei Fu, Benjamin W. Vandermeer, et al. *Handling Continuous Outcomes in Quantitative Synthesis.* Rockville,.

21. Higgins JPT. *Cochrane handbook for systematic reviews of interventions.* Wiley-Blackwell; 2020.
22. Madhu K, Chanda K, Saji MJ. Safety and efficacy of Curcuma longa extract in the treatment of painful knee osteoarthritis: a randomized placebo-controlled trial. *Inflammopharmacology.* 2013;21(2):129-136.
23. Shep D, Khanwelkar C, Gade P, Karad S. Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open-label parallel-arm study. *Trials.* 2019;20(1):214-225.
24. Shep D, Khanwelkar C, Gade P, Karad S. A Randomized Controlled Trial of Curcumin and Diclofenac Combination in Knee Osteoarthritis *Int J Curr Pharm Res.* 2019;11(6):111-114.
25. Shep D, Khanwelkar C, Gade P, Karad S. Efficacy and safety of combination of curcuminoid complex and diclofenac versus diclofenac in knee osteoarthritis: A randomized trial. *Medicine (Baltimore).* 2020;99(16):e19723.
26. • Henrotin Y, Malaise M, Wittoek R, et al. Bio-optimized *Curcuma longa* extract is efficient on knee osteoarthritis pain: a double-blind multicenter randomized placebo controlled three-arm study. *Arthritis Res Ther.* 2019;21(1):179. **This randomized trial is a recent randomized trial about tumeric for osteoarthritis that are of high-quality.**
27. Gupte PA, Giramkar SA, Harke SM, et al. Evaluation of the efficacy and safety of Capsule Longvida((R)) Optimized Curcumin (solid lipid curcumin particles) in knee osteoarthritis: a pilot clinical study. *J Inflamm Res.* 2019;12:145-152.
28. Furukawa TA, Barbui C, Cipriani A, et al. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol.* 2006;59(1):7-10.
29. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions. 2019:205-228.
30. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343(oct18 2):d5928-d5928.
31. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.
32. Stuck AE, Rubenstein LZ, Wieland D. Bias in meta-analysis detected by a simple, graphical test. Asymmetry detected in funnel plot was probably due to true heterogeneity. *BMJ.* 1998;316(7129):469.
33. Duval S, Tweedie R. A Nonparametric "Trim and Fill" Method of Accounting for Publication Bias in Meta-Analysis. *J Am Stat Assoc.* 2000;95(449):89-98.
34. Thompson SG, Higgins JPT. Can meta-analysis help target interventions at individuals most likely to benefit? *The Lancet.* 2005;365(9456):341-346.
35. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc A Stat.* 2009;172(1):137-159.
36. Nakagawa Y, Mukai S, Yamada S, et al. Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: a randomized, double-blind, placebo-controlled prospective study. *J Orthop Sci* 2014;19(6):933-939.
37. Panahi Y, Rahimnia A-R, Sharafi M, et al. Curcuminoid Treatment for Knee Osteoarthritis: A Randomized Double-Blind Placebo-Controlled Trial. *Phytother Res.* 2014;28(11):1625-1631.
38. Srivastava S, Saksena AK, Khattri S, et al. *Curcuma longa* extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial. *Inflammopharmacology.* 2016.
39. Haroyan A, Mukuchyan V, Mkrtchyan N, et al. Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. *BMC Complement Altern Med.* 2018;18(1).
40. Panda SK, Nirvanashetty S, Parachur VA, et al. A Randomized, Double Blind, Placebo Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of Curene® versus Placebo in Reducing Symptoms of Knee OA. *BioMed Res Int.* 2018;2018:1-8.
41. Hashemzadeh K, Davoudian N, Jaafari MR, et al. The Effect of Nanocurcumin on the Improvement Symptoms of Knee Osteoarthritis: A Randomized Clinical Trial. *Curr Rheumatol Rev.* 2020;16:0-0.
42. •• Zhiqiang W, Graeme J, Tania W, et al. Effectiveness of *Curcuma longa* extract for the treatment of symptoms and effusion-synovitis of knee osteoarthritis: a randomized trial. *Ann Intern Med.*

2020. **This study provides a high-quality evidence on efficacy and safety of *Curcuma longa* extract for the treatment of knee OA.**
43. Kuptniratsaikul V, Thanakhumtorn S, Chinswangwatanakul P, et al. Efficacy and Safety of *Curcuma domestica* Extracts in Patients with Knee Osteoarthritis. *J Altern Complement Med.* 2009;15(8):891-897.
44. Kertia N. Ability of Curcuminoid Compared to Diclofenac Sodium in Reducing the Secretion of Cycloxygenase-2 Enzyme by Synovial Fluid's Monocytes of Patients with Osteoarthritis. *Acta Med Indones.* 2012.
45. Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, et al. Efficacy and safety of *Curcuma domestica* extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. *Clin Interv Aging.* 2014:451.
46. Kertia N. Anti-inflammatory activities and the safety of curcuminoid from curcuma domestica val. Rhyzome extract compared to diclofenac sodium for the treatment of Osteoarthritis. International Conference and Exhibition on Pharmacognosy, Phytochemistry & Natureal Products; 2013; Hyderabad, India.
47. Panahi Y, Alishiri GH, Parvin S, et al. Mitigation of Systemic Oxidative Stress by Curcuminoids in Osteoarthritis: Results of a Randomized Controlled Trial. *J Diet Suppl.* 2015;13(2):209-220.
48. Rahimnia AR, Panahi Y, Alishiri G, et al. Impact of Supplementation with Curcuminoids on Systemic Inflammation in Patients with Knee Osteoarthritis: Findings from a Randomized Double-Blind Placebo-Controlled Trial. *Drug Res (Stuttg).* 2015;65(10):521-525.
49. Wu J, Lv M, Zhou Y. Efficacy and side effect of curcumin for the treatment of osteoarthritis: A meta-analysis of randomized controlled trials. *Pak J Pharm Sci.* 2019;32(1):43-51.
50. White CM, Pasupuleti V, Roman YM, et al. Oral turmeric/curcumin effects on inflammatory markers in chronic inflammatory diseases: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res.* 2019;146:104280.
51. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr Cartil.* 2014;22(3):363-388.
52. Gregori D, Giacovelli G, Minto C, et al. Association of Pharmacological Treatments With Long-term Pain Control in Patients With Knee Osteoarthritis. *JAMA.* 2018;320(24):2564.
53. Roberts E, Delgado Nunes V, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis.* 2016;75(3):552-559.
54. Fine M. Quantifying the impact of NSAID-associated adverse events. *Am J Manag Care.* 2013;19(14):s267-272.