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Efficacy of Extracts of Oleogum Resin of *Boswellia* in the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-Analysis

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ABSTRACT

Knee osteoarthritis (OA) has recently been ranked as the 11th highest contributor to global disability. More than 40% of patients use complementary and alternative medicine including supplements containing phytoextracts with anti-inflammatory properties as those from the *Boswellia* genus. The aim of this meta-analysis was to evaluate the efficacy of phytoextracts from the oleogum resin of the *Boswellia* genus as supplementation for patients affected by knee OA. Four electronic databases were used for the research and PRISMA statements were followed throughout the study. The following inclusion criteria were used: (a) the subjects of the study were humans with a diagnosis of knee OA reported by medical staff; (b) randomization and the presence of control (placebo, negative or positive control), and (c) outcomes reported with WOMAC and/or visual analog scale (VAS) score. Publication bias was assessed with a funnel plot and through the Egger test. The Jadad scale was used in order to assess the quality of the studies included. The statistical heterogeneity was assessed using I^2 statistics. Results of meta-analysis and subgroup analysis were reported using a forest plot. A total of 13 studies involving 850 (WOMAC) and 1185 (VAS) patients met the inclusion criteria. The meta-analysis did not detect a significant effect of the use of *Boswellia* extracts between the control and the treatment groups due to the high heterogeneity of the studies ($p = 0.0865$ for WOMAC) and ($p = 0.3966$ VAS). However, the subsequent subgroup analysis demonstrated the significant beneficial effect of *Boswellia* extracts in the treatment of knee OA with respect to a placebo (lower WOMAC score in the treatment groups). This was also confirmed in the meta-regression applied to the WOMAC scores. This is an important finding as people exposed to NSAID-related adverse effects could benefit from the use of *Boswellia* extracts. However, further high-quality studies are needed to establish the clinical efficacy of extracts from the genus *Boswellia*.

1 | Introduction

In 2019, 1.7 billion people worldwide lived with musculoskeletal pathologies, of these people, 528 million suffered from osteoarthritis (OA), leading to 19 million years lived with disability (YLD) (Cieza et al. 2019; Williams et al. 2018). Osteoarthritis is a chronic inflammatory disease characterized by a reduction in mobility that involves the joints, causing pain and stiffness. It is a common disease in adult people over 55 years of age, with a higher prevalence in women, and it is related to other diseases, such as obesity and diabetes mellitus (Paul et al. 2022). A prevalence of OA of 10% in men and 18% in women has been estimated in adults over 60 years of age, and it is expected that, in 2050, 130 million people will suffer from musculoskeletal diseases (Bolognesi et al. 2016). Knee OA has recently been ranked as the 11th highest contributor to global disability (Cross et al. 2014).

As reported by Colletti and Cicero the approaches in the treatment of OA include pharmacological intervention with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitor drugs, lifestyle changes associated with physical activity, and the rehabilitation and application of a specific nutritional plan (Colletti and Cicero 2021). Nevertheless, if the above-mentioned approaches do not provide any benefit, the latest possibility in the treatment of this disease is surgery. The Western Ontario and McMaster University (WOMAC) score is a recommended patient-recorder outcome (PRO) used in the evaluation of treatment goals for hip and knee osteoarthritis (Peter et al. 2011). The WOMAC score is composed of three items: pain (5 questions), stiffness (2 questions), and physical function (17 questions); each question offers a score from 0 to 4, with 0 scored as none and 4 as extreme. The subscale scores can vary, with pain ranging from 0 to 20 points; stiffness, from 0 to 8 points; and physical function, from 0 to 68 points for a total score which can range from 0 to 96 points. Higher scores represent worse pain, stiffness, and functional limitations (Barber-Westin and Noyes 2017). As reported by Woolacott, Corbett, and Rice (2012), improved adherence to the standard use of the WOMAC scoring system, with clear reporting of it in trials of OA of the knee should be encouraged. The VAS is a unidimensional measure of pain intensity. It is made up of a horizontal (HVAS) or vertical (VVAS) 10-cm scale which has been widely used in different adult populations, including those with rheumatic or musculoskeletal diseases (Hawker et al. 2011). The scale score can vary from 0 (no pain) to 100 (worst imaginable pain) and is usually reported in cm from 0 to 10. The WOMAC and the VAS scores are often used together for assessing the degree of knee OA and the likely efficacy of a treatment.

Due to the possible adverse effects on the cardiovascular system of the drugs used in the standard management and the limited efficacy of the therapies available, more than 40% of patients with knee OA use complementary and alternative medicine (CAM) which also includes supplements containing phytoextracts with anti-inflammatory properties (Vina et al. 2021; Basedow, Runciman, and March 2014). Extracts from the gum resin of plants of the genus *Boswellia* (family Burseraceae), also known as frankincense or guggal, have been used in traditional Ayurvedic medicine for the treatment of inflammation, including OA (Abdel-Tawab, Werz, and Schubert-Zsilavecz 2011; Ammon 2006, 2016; Efferth and Oesch 2022). These extracts contain a plethora of bioactive molecules, including boswellic acids. Of these, 3-acetyl-11-keto-β-boswellic acid (AKBA), 11-keto-β-boswellic acid (KBA), and β-boswellic acid (BA) are well known for their biological activity in vitro and in vivo (Efferth and Oesch 2022; Bertocchi et al. 2018). Boswellic acids act by inhibiting 5-lipoxigenase (5-LO) and are also involved in inhibiting the prostaglandin synthesis of COXs and modulating the immune system (Ammon 2010). Given this premise, there are suggestions to use extracts from the resin of the genus *Boswellia* in treating anti-inflammatory diseases, including knee OA (Efferth and Oesch 2022).

A recent systematic review and meta-analysis carried out by Yu et al. (2020) analyzed the effectiveness of *Boswellia* extracts for the treatment of OA in seven randomized controlled trials. Based on the results of this meta-analysis, *Boswellia* and its extracts could be considered to be an effective option for patients affected by OA (Yu et al. 2020). However, the authors did not consider that, of the seven studies included, three did not use extracts but pure boswellic acids, and four used a combination with other bioactive molecules. In fact, many studies investigating the beneficial effects of *Boswellia* extracts use a combination with other plant extracts having anti-inflammatory properties, such as *Curcuma longa*, *Zingiber officinalis*, *Witamnia somnifera*, and *Harpagophytum procumbens*, or used in association with standard management treatments (Belcaro et al. 2018; Sharkey et al. 2021; Dragos et al. 2017). Finally, due to the aforementioned causes, the studies published so far were heterogeneous, and the scientific quality was often not satisfactory; therefore, data regarding the use of *Boswellia* extracts in the treatment of OA were contradictory.

The aim of this meta-analysis was to evaluate the efficacy of phytoextracts from the oleogum resin of the *Boswellia* genus as supplementation for knee OA patients. Due to the heterogeneity of the studies in the literature, a subgroup analysis was carried out, and a meta-regression approach was used to investigate the role of exclusively using extracts from *Boswellia* or using them in combination with other phytoextracts, and whether the type of control (placebo, negative, or positive control) and the duration of the treatment could affect the outcomes.

2 | Materials and Methods

2.1 | Search Strategy

The statements reported in Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 were followed throughout the study (Hoffmann et al. 2020).

Four electronic databases were used for this research: PubMed, MEDLINE, Cochrane Library, and SCOPUS. The keywords used included (*Boswellia* OR Frankincense OR Salai guggal OR Shallaki) AND (Knee Osteoarthritis OR Knee OA OR Osteoarthritis OR OA OR Arthritis OR joint OR Skeletal OR Musculoskeletal OR Bones OR Joint). Furthermore, the search was widened, taking into consideration all the references of the articles selected. The search was carried out from December 2022 to February 2023. No registration number was provided for the review protocol.

2.2 | Eligible Criteria and Study Selection

Each article satisfying the following inclusion criteria was included in the meta-analysis: (a) the subjects of the study were humans with a diagnosis of knee OA reported by medical staff; (b) randomization and the presence of control (placebo, negative or positive control), (c) outcomes reported with both WOMAC and VAS scores, or at least one of them, and (d) *Boswellia* extracts, an herbal formulation containing *Boswellia* and pure boswellic acids have been included in the analysis.

The exclusion criteria were: (a) any study with subjects suffering from OA without indication of the specific region of the body; (b) the presence of concomitant diseases; (c) studies that used

baseline (control group and treatment group was composed by the same subjects at different time period, usually before the treatment and at the end of the study) as control; (d) studies which did not report, or reported an incomplete, WOMAC or VAS score, and (e) short papers, case reports, reviews, and studies without English translation available.

Three authors (T.D., C.R., and G.A.) independently selected the studies by title and reviewed the abstracts of the articles selected. Studies that did not meet the predefined inclusion criteria were excluded. Any divergence in the study selection was dealt with by a co-author (G.I.) and was subsequently resolved.

2.3 | Data Extraction

The data from each study were independently extracted by two authors (T.D. and C.R.) under the supervision of two co-authors (G.I. and G.A.). In the case of missing data, the corresponding author of each study was contacted by email, and no one replied. When the studies provided only the standard error mean (SEM), the standard deviation (SD) was calculated using the following equation:

$$\mathrm{SD} = \mathrm{SEM} / \sqrt{n}$$

The Jadad scale was used to evaluate the methodological quality of the studies selected. The Jadad scale is a three-item assessment scale and the score is based on randomization (0 to 2 points), blinding (0 to 2 points), and account of all patients (0 to 1 point). Authors included in meta-analysis studies that showed at least a three-point judgment on the Jadad scale. The score of the studies is reported in Table 1. When studies used more than a single control group, a different posology, or different types of supplements in the groups treated, they were split and treated as separate data sets in the meta-analysis. In the case of studies that had more than one follow-up, they were split and treated as suggested by Dunlap et al. (1996). Additional information is reported in the 2.5 Statistical Analysis section. The table of the Jadad scale is reported in Figure S1.

2.4 | Risk of Bias Assessment

The risk of bias (RoB) assessment was done through the RoB 2 tool. As reported by Sterne et al. (2019), assessment of the risk of bias is considered an essential component of a systematic review, and the most commonly used tool for randomized trials is the Cochrane RoB tool. The tool is composed considering biases that can arise at different stages of a trial. Thus, based on both empirical evidence and theoretical considerations, the tool identified five bias domains. Judgments in the RoB 2 tool are provided by algorithms based on answers to the signaling questions of every domain of bias. Rob 2 analysis of WOMAC and VAS scores is reported below in Figures 1 and 2, respectively.

2.5 | Statistical Analysis

An all-time point standard mean difference (SMD) meta-analysis was carried out to take into consideration likely outcomes at every time point of the studies. As reported by Dunlap et al. (1996), if an effect size resulted after the statistical test without taking the correlation between the repeated measures into account, the effect size would be overestimated in studies with a repeated measures design. Furthermore, Dunlap et al. (1996) suggested that, in a repeated measures design study, the effect size should be calculated using an equation that takes into consideration the correlation r between every follow-up (Equation 1). Conversely, when the correlation between measures is not provided, the meta-analyst must use the means and SD to estimate effect size directly with the equation provided using Cohen's method (Equation 2) (Dunlap et al. 1996; Cohen 1988). Moreover, in a Montecarlo simulation with 10,000 iterations, it was shown that the differences in the effect size between the two equations were quite small, calculating with very similar outcomes as the sample size was bigger (Dunlap et al. 1996). Due to the lack of the correlation r coefficient in the studies taken into consideration in the meta-analysis, the effect size was calculated using Cohen's d method (Cohen 1988). The two equations mentioned above are reported below.

$$\mathrm{D\ (effect\ size)} = \mathrm{tc}\left[2\,(1-r)/n\right]^{1/2} \quad (1)$$

Equation (1): The equation suggested by Dunlap et al. for calculating effect size using a repeated measures study design. tc = t statistic for matched groups, r = correlation across pairs of measures, n = sample size (Dunlap et al. 1996).

$$\mathrm{D\ (effect\ size)} = (\mathrm{Me} - \mathrm{Mc})\,/\,\mathrm{SD} \quad (2)$$

Equation (2): The equation suggested by Cohen et al. for calculating effect size. Me = mean of the experimental group, Mc = mean of the control group, SD = common standard deviation (Dunlap et al. 1996; Cohen, 1988).

However, in all the studies with repeated measures that were taken into consideration, a correlation was not provided. Hence, the corresponding author of each study was contacted by email, and no one replied to give additional information regarding the data elaboration.

When a study presented more than one control, all the controls were considered separately in the meta-analysis. A control without any bioactive compounds was considered to be a "placebo," a formulation containing phytoextracts or bioactive compounds (except for those from *Boswellia*) was considered to be a "negative control," and a formulation used as standard management in the treatment of knee OA was considered to be a "positive control." In the presence of multiple treatments with *Boswellia* within a study, the different dosage groups were considered to be different treatment groups.

The presence of publication bias was assessed using the Egger test (Egger and Smith 1997) and the evaluation of the funnel plots. As reported by Sterne et al., tests for funnel plot asymmetry should be used when there are more than 10 studies (Sterne et al. 2011). The statistical heterogeneity was assessed using I^2 statistics. Heterogeneity was classified across the studies as low (< 30%), moderate (31% to 60%), substantial (61% to 74%), and considerable (> 75%) (Higgins et al. 2019). Random models were used owing to the heterogeneity. Data previously normalized on a

TABLE 1 | Characteristics and the Jadad scale score of the studies included in the meta-analysis based on design, treatment, posology, follow-up, type of control, and score provided. The numbers of the split data sets are reported in parentheses.

Author	Year	*N*	Study design	Treatment	Posology	Time points	Control	Score	Jadad scale score
Chopra et al. (2004) (30a, 30b)	2004	78 First time point 62 second time point	Randomized double-blind comparative trial	Herbal formulation with *Boswellia*	2 tablets per day (dosage of *B. serrata* not provided)	4 months 8 months	Placebo	WOMAC and VAS	4
Chopra et al. (2013) (31a, 31b, 31c)	2013	418	Randomized double-blind comparative trial	Herbal formulation with *Boswellia*	6 tablets per day (*B. serrata* oleoresin hydroalcoholic extract 100 mg per tablet)	6 months	Positive control, negative control	VAS	5
Haroyan et al. (2018) (32a, 32b, 32c, 32d)	2018	188 first time point 178 second time point	Randomized double-blind comparative trial	Herbal formulation with *Boswellia*	500 mg capsules 3 times per day (*B. serrata* 150 mg gum resin extract containing 75% of boswellic acids)	1 month 3 months	Placebo, negative control	WOMAC	5
Karimifar et al. (2017) (33a, 33b)	2017	75	Randomized double-blind controlled trial	Herbal formulation with *Boswellia*	200 mg/day with negative control 400 mg/day with positive control (*B. thurifera* 100 mg oleogum resin hydroalcoholic extract containing 70% of boswellic acids)	1 month	Positive control, negative control	VAS	3
Karlapudi et al. (2018) (34a, 34b, 34c, 34d, 34e, 34f, 34g, 34h)	2018	96	Randomized double-blind controlled trial	Herbal formulation with *Boswellia*	200 mg/day 400 mg/day (*B, serrata* extract with 0.6% of AKBA)	14 days 1 month 2 months 3 months	Placebo	WOMAC and VAS	4
Karlapudi et al. (2021)	2021	67	Randomized double-blind controlled trial	*Boswellia*	100 mg/day (*B. serrata* oleogum resin extract containing 20% of AKBA)	1 month	Placebo	WOMAC and VAS	5
Majeed et al. (2019)	2019	42	Randomized double-blind controlled trial	*Boswellia*	2 tablets/day (*B. serrata* extract 169.33 mg containing 87.3 mg of β-boswellic acids)	4 months	Placebo	WOMAC and VAS	5

(Continues)

TABLE 1 | (Continued)

Author	Year	*N*	Study design	Treatment	Posology	Time points	Control	Score	Jadad scale score
Notarnicola et al. (2011) (37a, 37b)	2011	60	Randomized trial	Dietary supplement with boswellic acids	2 sachets/day (5 g MSM 7.2 mg boswellic acids per sachet)	2 months 6 months	Placebo	VAS	4
Notarnicola et al. (2016) (38a, 38b)	2016	120	Randomized trial	Dietary supplement with boswellic acids	2 sachets/day (5 g MSM 7.2 mg boswellic acids per sachet)	2 months 6 months	Postive control (glucosamine sulfate)	VAS	4
Sengupta et al. (2008) (39a, 39b)	2008	70	Randomized double-blind controlled trial	*Boswellia*	100 mg/day 250 mg/day (*B. serrata* extract enriched with 30% AKBA)	3 months	Placebo	WOMAC and VAS	5
Sengupta et al. (2010) (40a, 40b)	2010	57	Randomized double-blind controlled trial	*Boswellia*	100 mg/day (*B. serrata* extract enriched with 30% AKBA) 100 mg/day (formulation 2: (*B. serrata* extract enriched with 20% AKBA	3 months	Placebo	WOMAC and VAS	5
Sharkey et al. (2021)	2021	43	Randomized double-blind trial	Herbal formulation with *Boswellia*	4 tablets/day (not provided the amount of *B. serrata*)	3 months	Placebo	WOMAC and VAS	3
Sontakke et al. (2007) (41a, 41b, 41c, 41d, 41e, 41f)	2007	66	Randomized trial	*Boswellia*	3 capsules/day (333 mg of *Boswellia serrata* extract containing 40% of boswellic acids per capsule)	1 month 2 months 3 months 4 months 5 months 6 months	Positive control (valdecoxib)	WOMAC	3
Vishal, Mishra, and Raychaudhuri (2011)	2011	59	Randomized double-blind controlled trial	*Boswellia*	100 mg/day (*B. serrata* extract containing 20% of boswellic acids)	1 month	Placebo	WOMAC and VAS	5

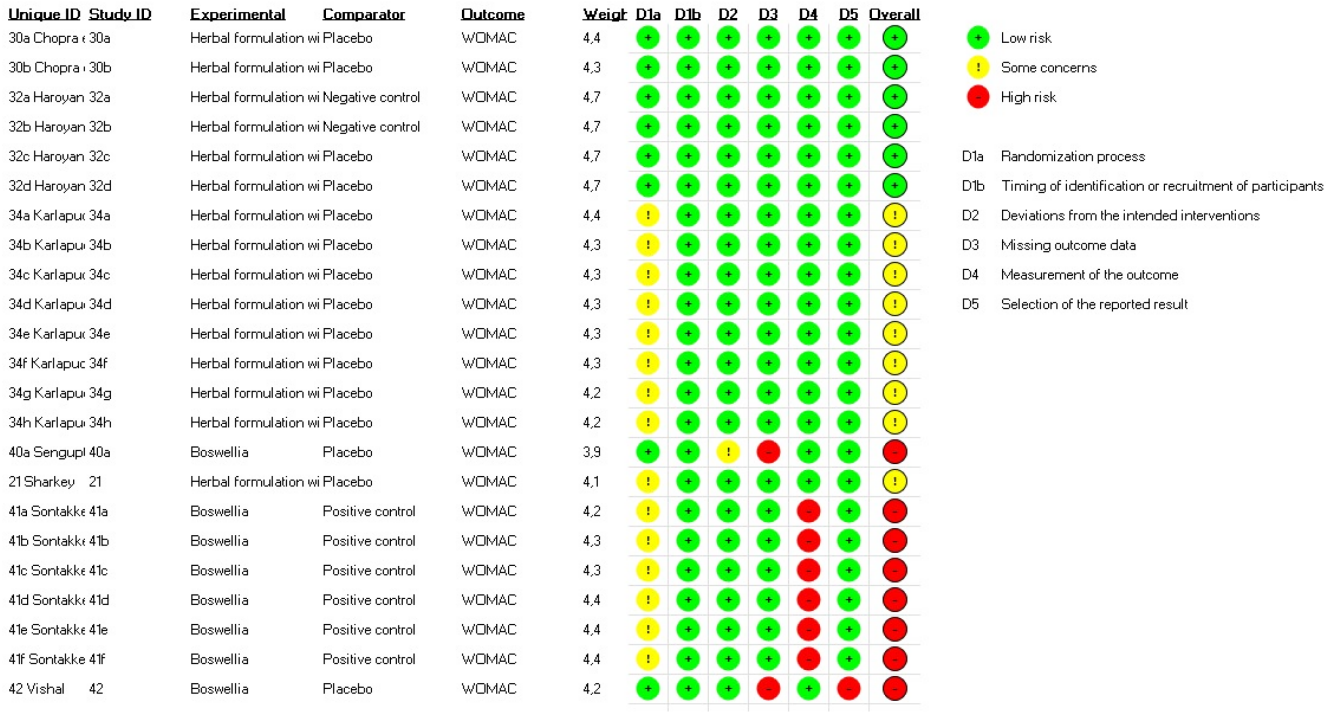

FIGURE 1 | Rob 2 analysis of the WOMAC score.

0 to 100 scale were converted to WOMAC (0 to 96) and VAS score (0 to 10) ranges. Subsequently, subgroup analyses were carried out among the types of controls, the types of treatment, and the duration of the studies (all the time points were taken into consideration) in order to minimize the impact of the heterogeneity.

A meta-regression approach using the controls, the types of treatment, and the duration of the studies was used to evaluate whether the variables were statistically significant and whether they affected the outcome of the studies. Differences were considered to be statistically significant for $p < 0.05$.

The statistical analyses were carried out using R 4.2.2 (R foundation for statistical computing; Vienna, Austria; https://www.R-project.org/, Accessed on May 1, 2023).

3 | Results and Discussion

3.1 | Search Results

Two hundred and twelve potential studies were found in the primary search. After a careful analysis based on the inclusion criteria, 159 studies were excluded, and 53 studies were selected (Figure 3). Of these, 38 were excluded for the following reasons: The concomitant presence of pathologies other than OA, data not extractable from the paper, and lacking WOMAC or VAS scores.

A total of 15 studies met the inclusion criteria, 11 studies (30 separate data sets taking into consideration controls, treatments, and time points) reported the WOMAC score and 12 studies (27 separate data sets taking into consideration controls, treatments, and time points) reported the VAS score. The search selection process is reported in Figure 3.

3.2 | Characteristics of the Studies

The characteristics of the studies included in the present meta-analysis are reported in Table 1.

The studies were published between 2004 and 2021. They were carried out in Italy, India, Armenia, Iran, and the United States.

To sum up, 820 patients were eligible when considering the inclusion criteria for the WOMAC score analysis and 1185 for the VAS score analysis.

In the WOMAC score analysis, six studies used supplements containing only extracts from *Boswellia*, five studies used an herbal formulation containing other extracts in addition to *Boswellia*, and of these, one used an herbal formulation containing *Boswellia* in association with a standard management drug. Of these 11 studies, two used a positive control, eight used a placebo as a control and the remaining one used both a placebo and a negative control. Regarding the duration of the trial, three studies lasted up to a maximum of 2 months, six studies lasted 4 months, one lasted 6 months and the remaining one lasted 8 months. Seven studies were organized with more than one follow-up, or more than one treatment was investigated or tested versus different types of control groups, the other four did not include multiple follow-ups, different treatments, or more than one control group.

In the VAS score analysis, five studies used supplements containing only extracts of *Boswellia*, while five studies used an herbal formulation containing other extracts in addition to *Boswellia* and two studies used a dietary supplement containing boswellic acids. Of these 12 studies, one used a positive control, nine

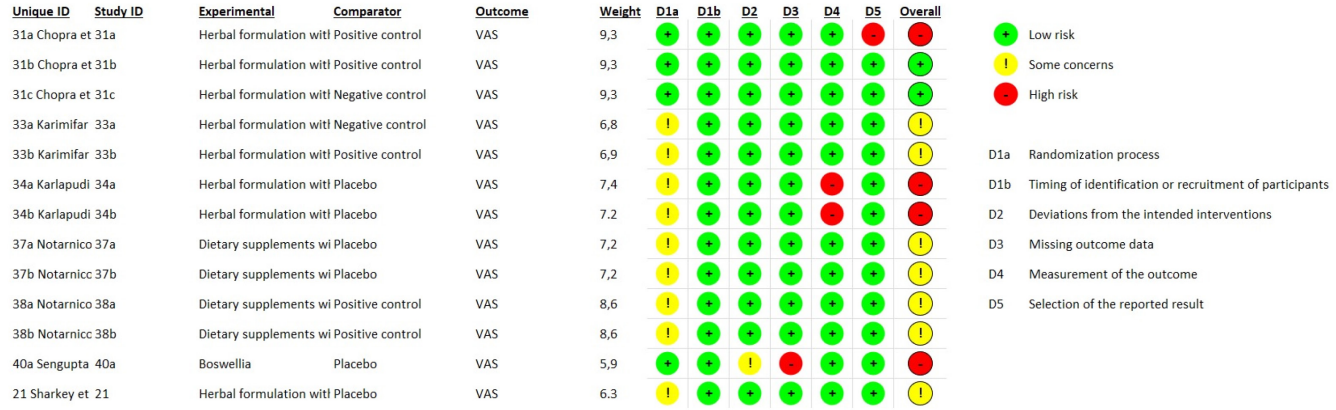

FIGURE 2 | Rob 2 analysis of the VAS score.

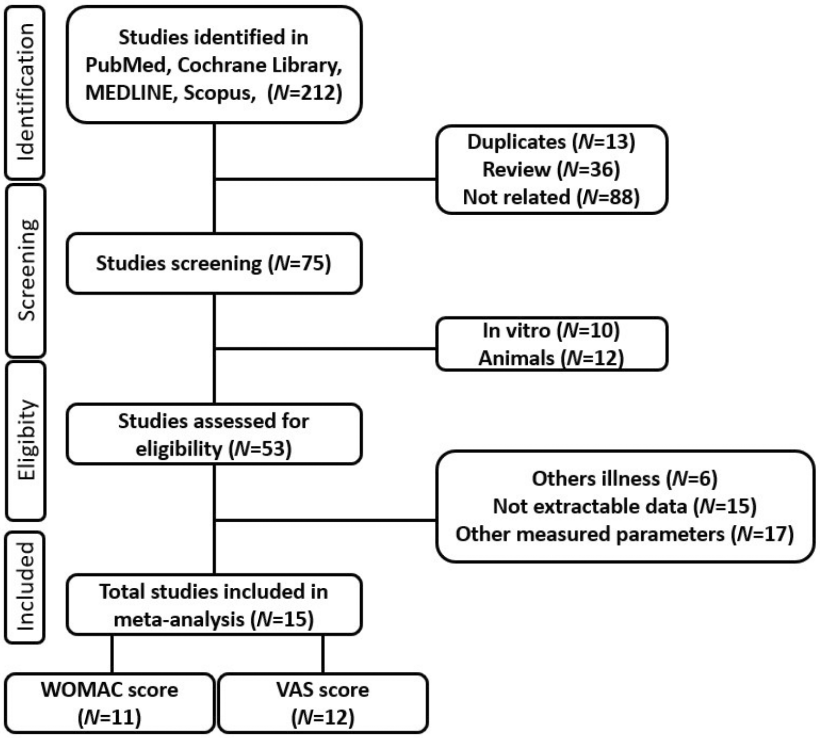

FIGURE 3 | PRISMA flowchart of the study selection process.

used a placebo, and the other two studies also included a negative control. Three studies analyzed for the VAS score lasted up to a maximum of 2 months, five studies lasted 4 months, three lasted 6 months and the remaining one lasted more than 6 months. Eight studies were organized with more than one follow-up, or more than one treatment was investigated or tested versus different types of control groups; the other four studies did not include multiple follow-ups, different treatments, or more than one control group.

3.3 | Publication Bias and Heterogeneity Percentage

The publication bias was measured using the Egger test for linear regression of funnel plot asymmetry. A significant publication bias was found in both the WOMAC ($p < 0.0001$) and the VAS score ($p < 0.0001$) groups. Thus, the presence of publication bias was resolved by removing the data sets one by one and repeating the Egger test at each step and by means of the visualization of the funnel plot. The data sets responsible for the asymmetry were: 4a, 4b, 30a, 30b, 35, 36, 39a, 39b, 40b for the WOMAC score, and 30a, 30b, 34c, 34d, 34e, 34f, 34g, 34h, 35, 36, 39a, 39b, 40b, 35 for the VAS score. These data sets were not included in the meta-analysis. The funnel plots for the WOMAC and the VAS scores are reported in Figures 4 and 5, respectively.

Consequently, the meta-analysis was carried out on 6 studies (split into 20 data sets, 32a, 32b, 32c, 32d, 34a, 34b, 34c, 34d, 34f, 34g, 34h, 40a, 21, 41a, 41b, 41c, 41d, 41e, 41f, 42) and seven studies (split into 13 data sets, 31a, 31b, 31c, 33a, 33b, 34a,

34b, 37a, 37b, 38a, 38b, 40a, 21) with 568 and 869 patients for the WOMAC and the VAS scores, respectively ($p = 0.0603$, $p = 0.0589$).

The heterogeneity was checked using the I^2 test. A heterogeneity percentage of 85.0% for the WOMAC score and 75.5% for the VAS score was detected; therefore, the use of random models was justified (Sterne et al. 2011). The heterogeneity of studies can be traced basically to three main causes: (1) different control types, (2) different supplement types, and (3) different duration of the trials; this was analyzed through subgroup analysis.

3.4 | WOMAC Score Meta-Analysis

The meta-analysis random model did not detect a significant effect of the use of *Boswellia* extracts between the control and the treatment groups ($p = 0.0865$, SMD = −0.2370, CI = −0.580 to 0.0340). The forest plot of the outcome of the meta-analysis for the WOMAC score is reported in Figure 6.

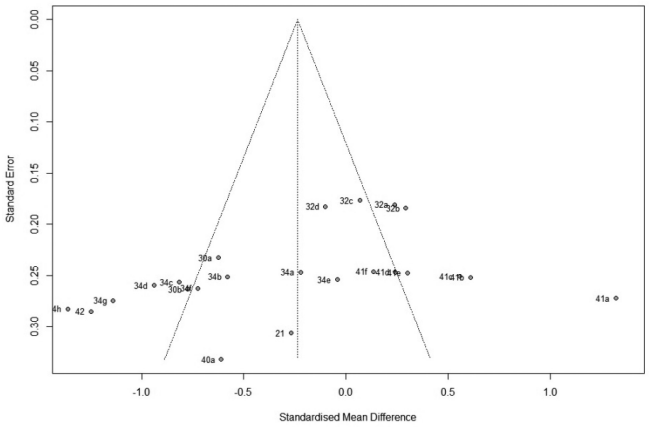

FIGURE 4 | Funnel plot for the WOMAC score (Egger test $p = 0.0603$). The numbers refer to the respective references.

In particular, 11 data sets (32a, 32b, 32c, 32d, 34a, 34e, 40a, 21, 41d, 41e, 41f) showed no significant effect between the treatment and the control groups. Conversely, 12 data sets (30a, 30b, 34b, 34c, 34d, 34f, 34g, 34h, 41a, 41b, 41c, 42) showed a significant effect. Of those, nine data sets (30a, 30b, 34b, 34c, 34d, 34f, 34g, 34h, 42) showed a lower WOMAC score in the treatment group, suggesting that the supplementation with *Boswellia* extracts might have produced beneficial effects in patients with knee OA. The last three data sets (41a, 41b, and 41c) showed a higher WOMAC score in the treatment group, suggesting a significant positive effect of the valdecoxib used in the positive control group (Sontakke et al. 2007).

3.5 | WOMAC Score Subgroup Analysis

Differences in the control groups, treatments, and time points were present in the studies used for the meta-analysis. In this case, a subgroup analysis should be used as a supportive and exploratory approach, as reported by Moyé and Deswal (2001), in order to understand which factors could influence the meta-analysis. Therefore, the subgroup analysis was carried out by splitting the studies based on the control type, treatment formulation, and duration of the study.

3.5.1 | WOMAC Score Subgroup Analysis Based on the Control Type

In the subgroup analysis based on different types of controls, three groups were identified: "positive control" indicating the use of a drug usually administered in the management of knee OA (41a, 41b, 41c, 41d, 41e, 41f), "placebo" indicating a control group which took a similar drug/formulation of the treatment group without any bioactive compounds (30a, 30b, 32c, 32d,

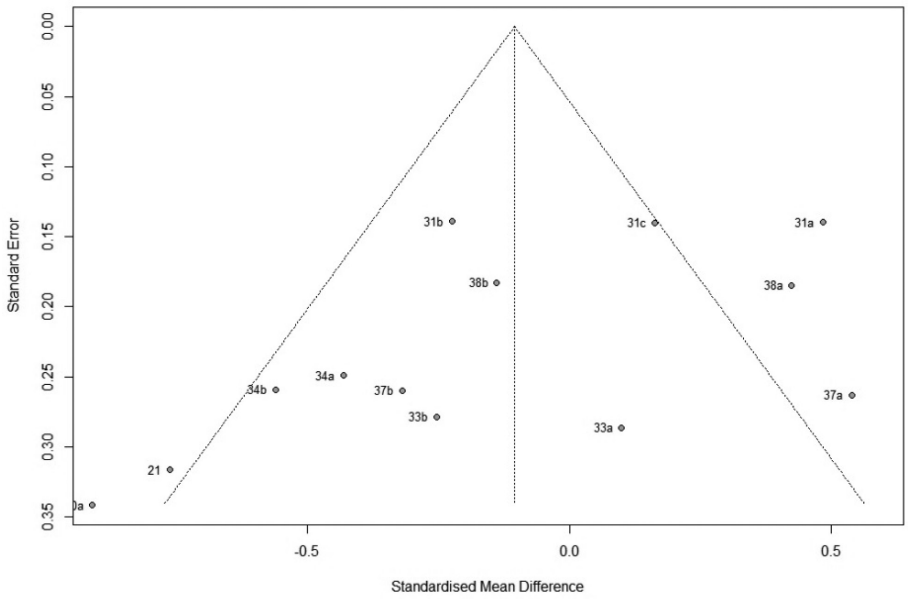

FIGURE 5 | Funnel plot for the VAS score (Egger test $p = 0.0589$). The numbers refer to the respective references.

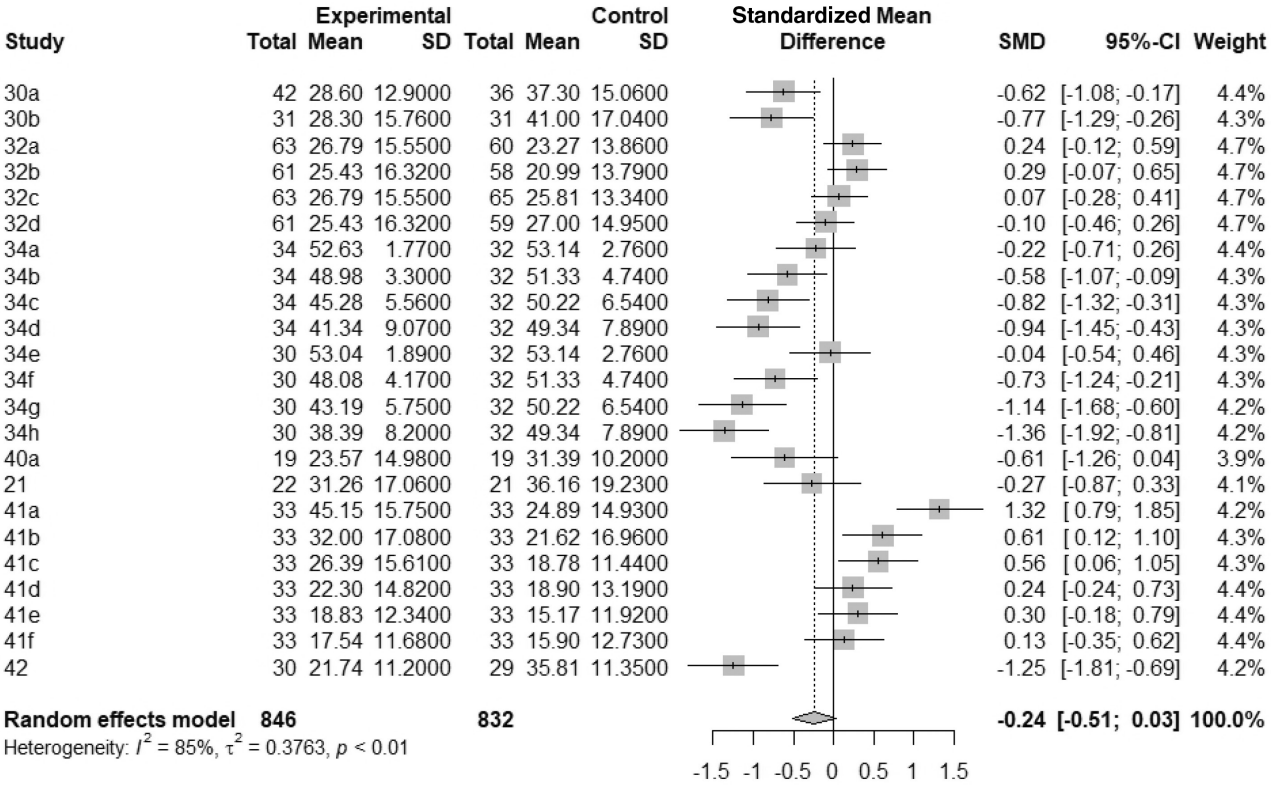

FIGURE 6 | Efficacy of *Boswellia* extracts in the management of knee OA: A forest plot of the outcome of the meta-analysis for WOMAC score between control and treatment groups in a standardized mean difference meta-analysis (SMD = −0.24, 95% CI = −0.51 to 0.03).

34a, 34b, 34c, 34d, 34e, 34f, 34g, 34h, 40a, 21, 42), and finally, "negative control" indicating the administration of the same formulation containing phytoextracts or bioactive compounds except those from *Boswellia* (32a, 32b). The outcome of the WOMAC score subgroup analysis based on the control type is reported in Figure 7.

Significant differences ($p < 0.0001$) were detected using the random effects model, showing a clear effect of the type of control used in the trial. A placebo was used in 15 data sets and showed a medium effect size (SMD = 0.5954), suggesting that the use of *Boswellia* produces an improvement in the treatment of knee OA with respect to the administration of no supplementation. Furthermore, studies that used a placebo in the control group make up 64.6% of the random model applied in the meta-analysis of the WOMAC score. The use of negative control (SMD = 0.2638) provided a small effect size, and no significant effect was detected, likely due to the fact that only one study (two different time points 32a, 32b) compared the effect of extracts of *Boswellia* and the administration of a formulation without it (Haroyan et al. 2018). Finally, the use of a positive control was reported by Sontakke et al. (2007) and a medium effect size was shown (SMD = 0.5111), suggesting that the drugs usually administered in the treatment of knee OA determined a lower WOMAC score with respect to the use of formulations containing extracts from the resin of *Boswellia*. In this study, the patients were followed at monthly time intervals for up to 6 months. Interestingly, the supplement containing the extract of *Boswellia* showed an onset slower than that of the conventional drug (valdecoxib); consequently, a significantly lower WOMAC score in the positive control group was measured during the first 3 months (41a, 41b, and 41c), while during the following 3 months (41d, 41e, 41f), no significant differences were recorded between the two groups.

3.5.2 | WOMAC Score Subgroup Analysis Based on the Supplement Type

In the subgroup analysis based on treatment type, two groups were detected: the use of mixed herbal formulations with *Boswellia* (30a, 30b, 32a, 32b, 32c, 32d, 34a, 34b, 34c, 34d, 34e, 34f, 34g, 34h, 21) and the use of a formulation exclusively containing an extract of *Boswellia* (40a, 41a, 41b, 41c, 41d, 41e, 41f, 42). The outcome of the WOMAC score subgroup analysis based on treatment types is reported in Figure 8.

Significant differences between the two groups were detected by the random effects model ($p = 0.0423$), showing a possible influence of the type of formulation used as a supplement in the trials. In particular, the use of an herbal formulation with *Boswellia* or the use of an extract of *Boswellia* exclusively showed a small (SMD = −0.4348) and a very small (SMD = 0.1725) effect size, respectively, suggesting that the exclusive presence of extracts from the gum resin of *Boswellia* produced just a mild improvement in the treatment of knee OA. Concerning the administration of an herbal formulation with *Boswellia*, eight of the 15 data sets considered showed a significant difference between the control and the treatment groups, with the latter showing a lower WOMAC score. In

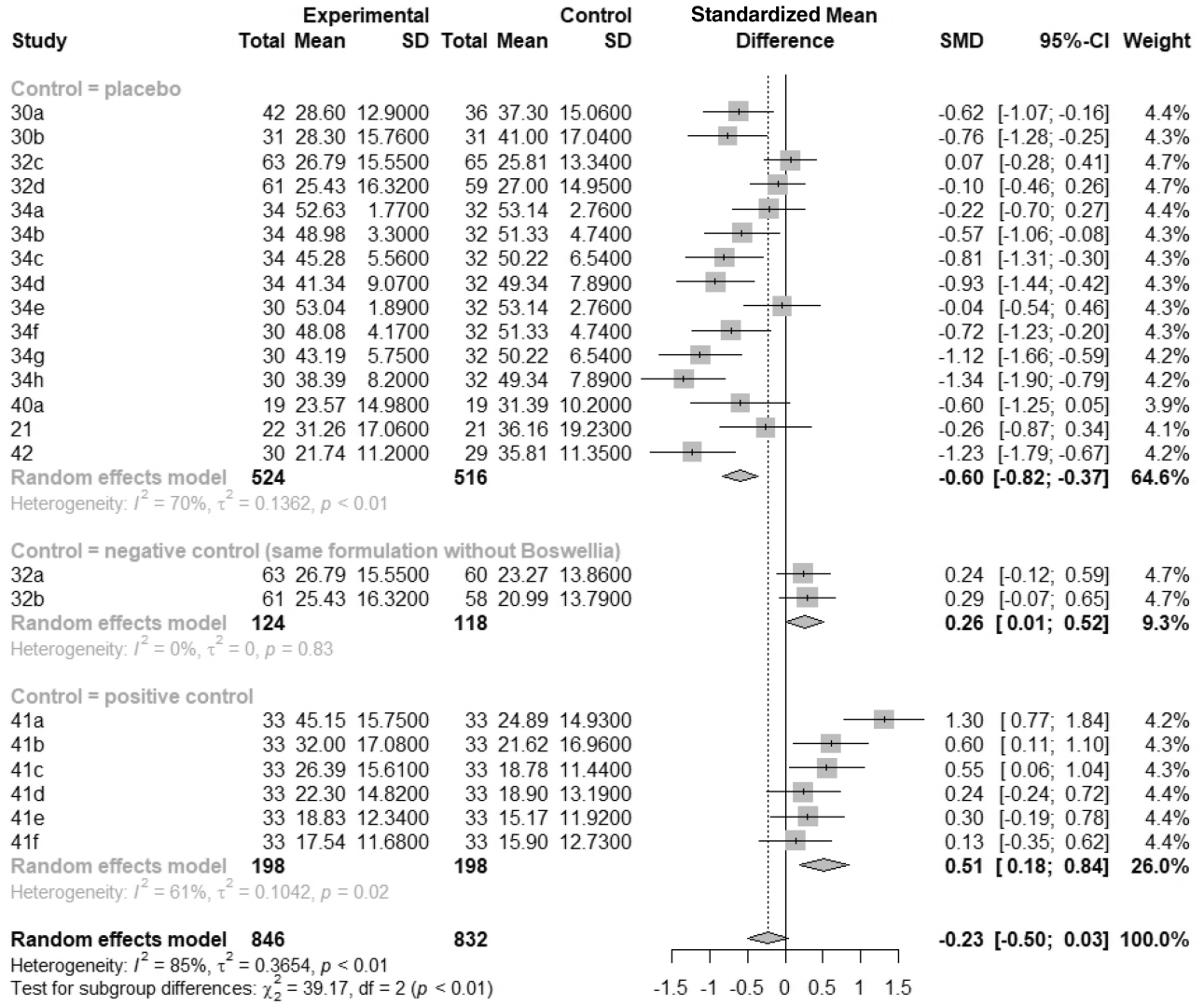

FIGURE 7 | Efficacy of *Boswellia* extracts in the management of knee OA: A forest plot of the WOMAC score subgroup analysis based on the control type.

contrast, regarding the exclusive use of an extract of *Boswellia*, only one study (42) showed a significantly lower WOMAC score in the treatment group, while another study (41, split into three data sets 41a, 41b, 41c) showed a significantly lower WOMAC score in the control group which, however, received NSAID as a positive control. These results suggested that other plants contributed to the beneficial effects or, alternatively, that a synergic effect between different phytoextracts could be hypothesized.

The authors emphasize that the result should be interpreted carefully; of note is that the only study (41) that compared the treatment groups with a positive control was in the subgroup of those using only *Boswellia*. Thus, it was not possible to evaluate and include in the meta-analysis studies comparing the administration of herbal formulations containing *Boswellia* bioactive compounds with a positive control. Furthermore, the use of an herbal formulation with *Boswellia* accounts for 65.9% of the random model applied in the meta-analysis of the WOMAC score.

3.5.3 | WOMAC Score Subgroup Analysis Based on the Duration of the Trial

In the subgroup analysis based on the duration of the trial, four groups were selected: 0–2 months (32a, 32c, 34a, 34b, 34c, 34e, 34f, 34g, 41a, 41b, 42), 3–4 months (30a, 32b, 32d, 34d, 34h, 40a, 21, 41c, 41d), 5–6 months (41e, 41f) and >6 months (30b). The outcome of the WOMAC score subgroup analysis based on the duration of the studies is reported in Figure 9.

Significant differences were detected by the random effects model among the four groups (p = 0.0159), highlighting the fact that the duration of the studies and the outcomes of each time point could influence the efficacy of the extracts of *Boswellia* in the treatment of knee OA. Except for the >6-month time period, all the studies showed a small size effect (SMD = −0.2208 in the 0–2 months period, 0.2921 in the 3–4 months period, and 0.2150 in the 5–6 months period, respectively). To the best of the authors' knowledge, Chopra et al. published the only study lasting more than 6 months and showed a medium-size effect

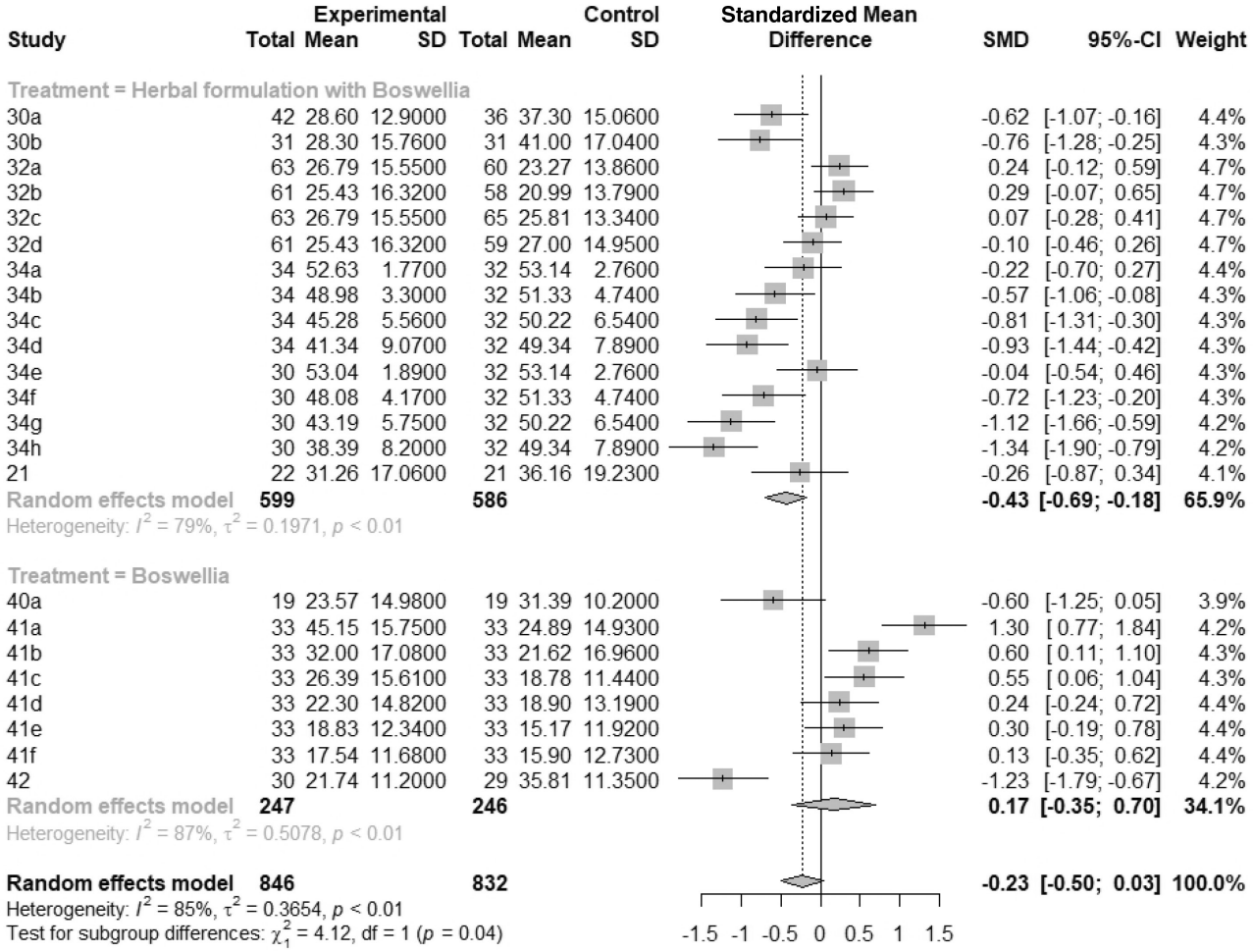

FIGURE 8 | Efficacy of *Boswellia* extracts in the management of knee OA: A forest plot of the WOMAC score subgroup analysis based on the treatment type.

(SMD = −0.7641) (30b). Due to the different outcomes shown in the studies which provided more than one time point, it is difficult to understand how time could affect the treatment of the disease when using *Boswellia*.

3.6 | VAS Score Meta-Analysis

The meta-analysis random model did not detect significant differences between the control and the treatment groups (p = 0.3966, SMD = −0.1049, 95% CI = −0.3473 to 0.1376). The forest plot of the VAS score meta-analysis is reported in Figure 10.

Seven data sets (31b, 31c, 33a, 33b, 34a, 37b, 38b) did not show significant differences. On the other hand, six data sets showed a significant effect (31a, 34b, 37a, 38a, 40a, 21). Of those, three showed a higher VAS score in the treatment group (31a, 37a, 38a); however, 37a and 38a did not use an extract of *Boswellia* but a supplement containing pure boswellic acids. The other three data sets (34b, 40a, 21) showed a higher VAS score in the control group demonstrating that, in the treatment of knee OA, the effects of extracts of *Boswellia* are contradictory.

3.7 | VAS Score Subgroup Analysis

As previously reported for the WOMAC score, a subgroup analysis was carried out, splitting the studies based on control types, treatment formulation, and duration of the study.

3.7.1 | VAS Score Subgroup Analysis Based on the Control Type

In the subgroup analysis based on different types of controls, three groups were identified: positive control (31a, 31b, 33b, 38a, 38b), placebo (34a, 34b, 37a, 37b, 40a, 21), and finally, negative control (31c, 33a). The outcome of the VAS score subgroup analysis is reported in Figure 11.

Significant differences among the groups were not detected by the random effects model (p = 0.0817), suggesting that different outcomes regarding the efficacy of *Boswellia* did not depend on the type of control. It should be noted that two data sets (31a, 38a) reported a lower VAS score in the positive control group, while another three data sets did not show significant differences between the control and the treatment groups. A negative control group was used in two studies, and no significant differences were detected in

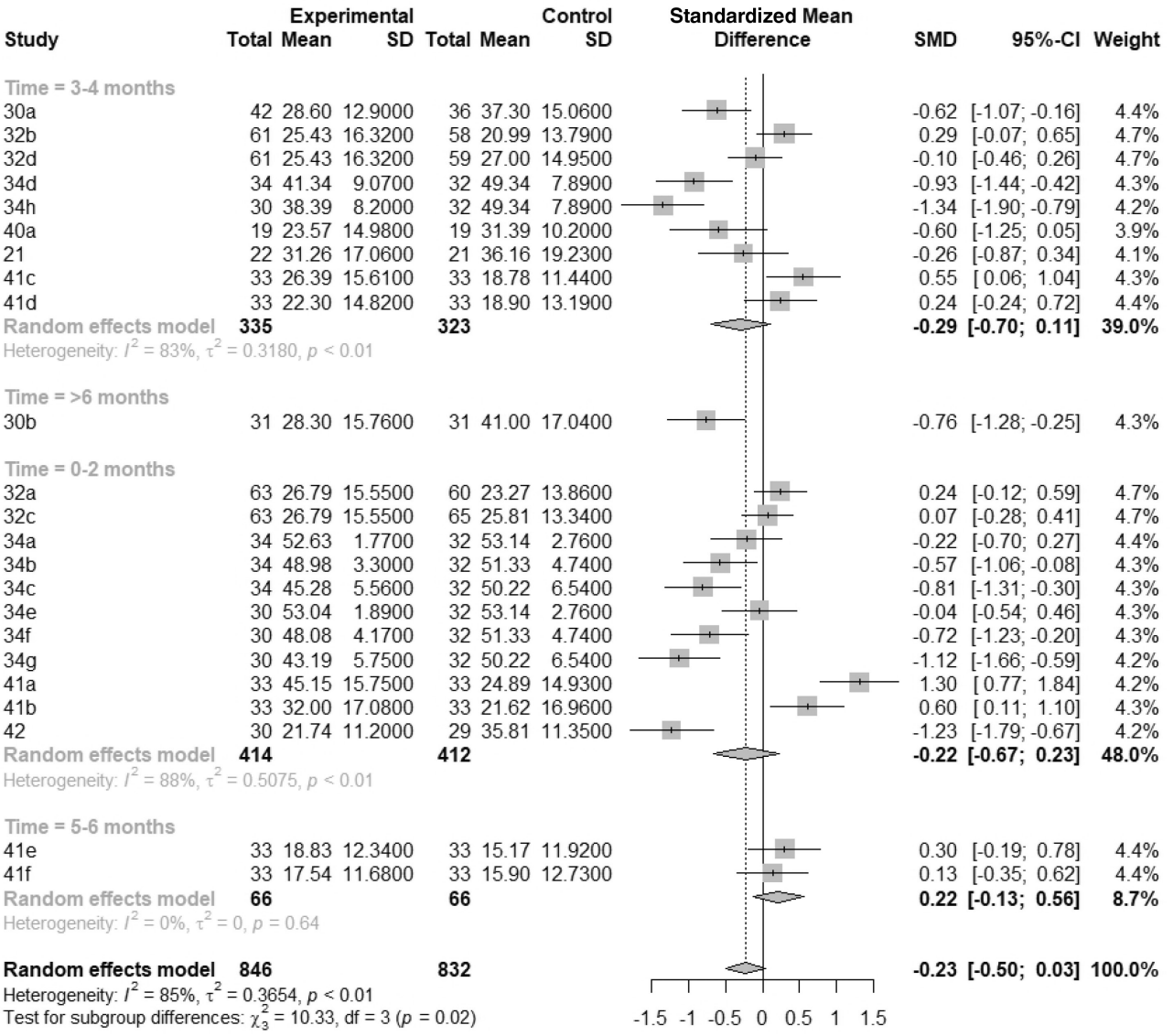

FIGURE 9 | Efficacy of *Boswellia* extracts in the management of knee OA: A forest plot of the WOMAC score subgroup analysis based on the duration of the studies including different time points.

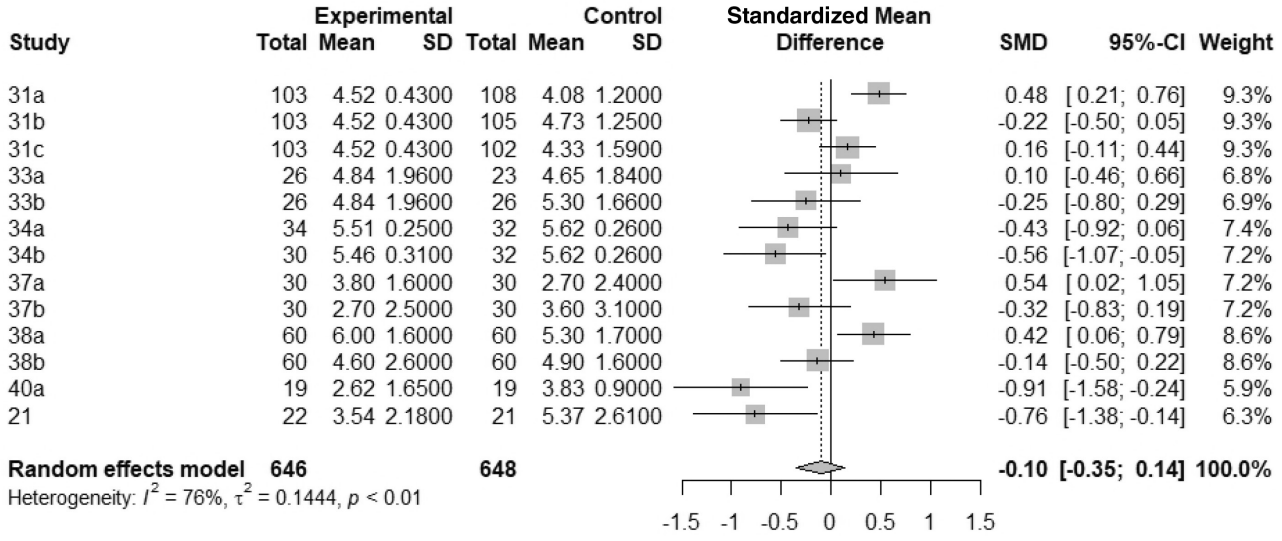

FIGURE 10 | Efficacy of *Boswellia* extracts in the management of knee OA: A forest plot of the VAS score between the control and the treatment groups in an SMD meta-analysis.

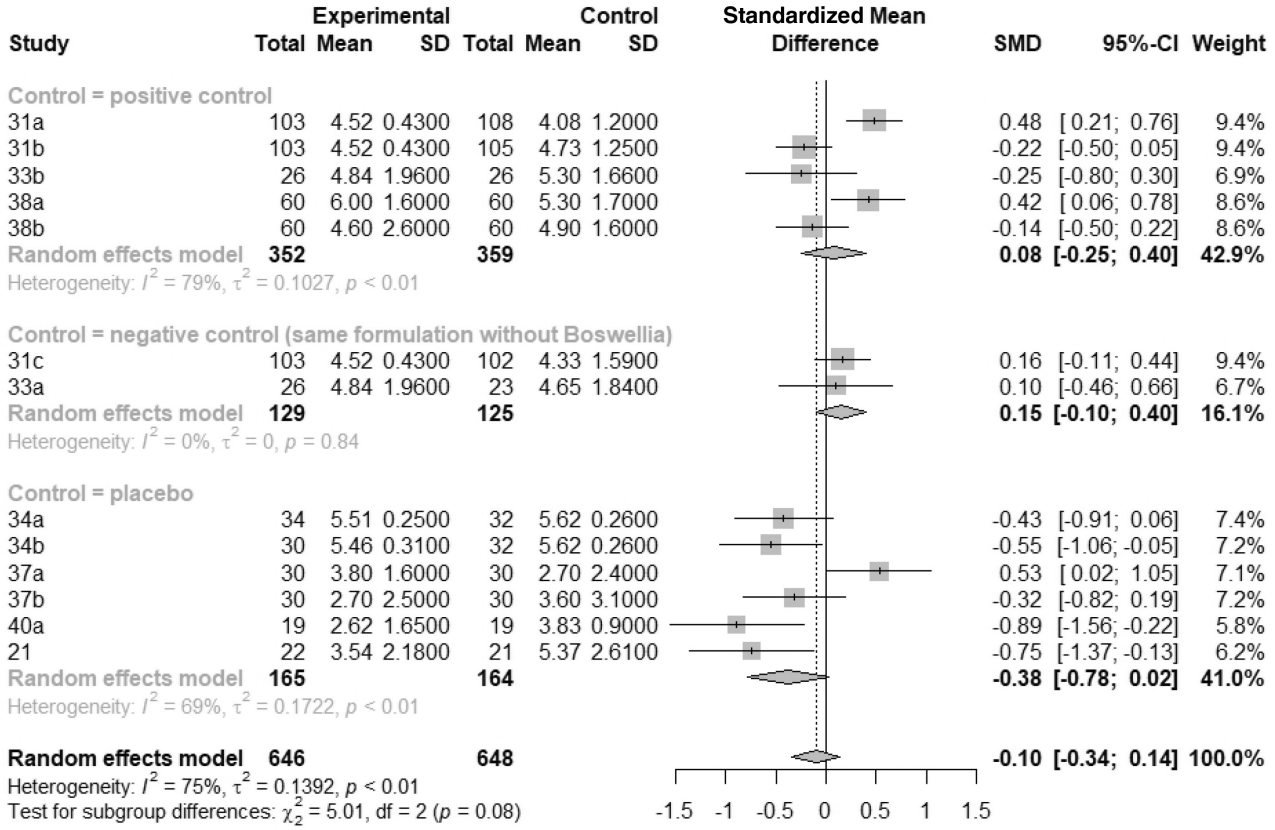

FIGURE 11 | Efficacy of *Boswellia* extracts in the management of knee OA: A forest plot of the VAS score subgroup analysis based on control type.

the VAS score with respect to the treatment group. Furthermore, the trials that used a placebo as a control group had contrasting outcomes with three studies detecting a lower VAS score in the treatment group (34a, 40a, 21), while another study reported a higher VAS score in the treatment group (37a) at the first follow-up but not at the second (Sharkey et al. 2021; Karlapudi et al. 2018; Notarnicola et al. 2011; Sengupta et al. 2010).

3.7.2 | VAS Score Subgroup Analysis Based on the Supplement Type

A subgroup analysis was carried out splitting the studies into three different groups: the use of herbal formulation with *Boswellia* (31a, 31b, 31c, 33a, 33b, 34a, 34b, 21), the use of a formulation exclusively containing extract of *Boswellia* (40a) and the use of a dietary supplement containing pure boswellic acids (37a, 37b, 38a, 38b). The outcome of the VAS score subgroup analysis based on treatment type is reported in Figure 12.

Only one study used a formulation exclusively containing a *Boswellia* extract (Sengupta et al. 2010). Significant differences among the three subgroups were detected ($p = 0.0371$); in fact, patients supplemented with the extract of *Boswellia* showed a significantly lower VAS score in the treatment group with respect to the placebo, suggesting that this type of formulation could be helpful in the treatment of patients with knee OA (Sengupta et al. 2010).

Of the studies which used an herbal formulation also containing *Boswellia* in association with other phytoextracts, five data sets did not show a significant difference among the groups (31b, 31c, 33a, 33b, 34a) and only two data sets showed a significantly lower VAS score in the treatment group (34b, 21), while only one data set showed a significantly higher score than the control group (31a). However, a small effect size was calculated regarding the use of an herbal formulation containing *Boswellia* (SMD = −0.1384). Notarnicola et al. (2011, 2016) were the only authors who investigated the use of dietary supplements containing pure boswellic acids; at the first time point of both studies (2 months) a significantly lower VAS score was determined in the control group (37a, 38a), while at the second time point (6 months), there was no significant difference in the VAS score between the treatment and the control groups (37b, 38b). A small effect size was detected in these studies which investigated the use of dietary supplements containing pure boswellic acids (SMD = 0.1256).

3.7.3 | VAS Score Subgroup Analysis Based on the Duration of the Trial

The subgroups were split as reported in 3.6.3, with the exception of the last group (> 6 months). To the best of the authors' knowledge, no research regarding the efficacy of *Boswellia* in the treatment of knee OA using VAS score has lasted longer than 6 months. Four studies (six data sets) lasted 0–2 months (33a, 33b, 34a, 34b, 37a, 38a), two lasted 3–4 months (40a, 21) and 3 (five data sets) lasted 5–6 months (31a, 31b, 31c, 37b, 38b). The forest plot of the VAS score subgroup analysis based on the duration of the trial is reported in Figure 13.

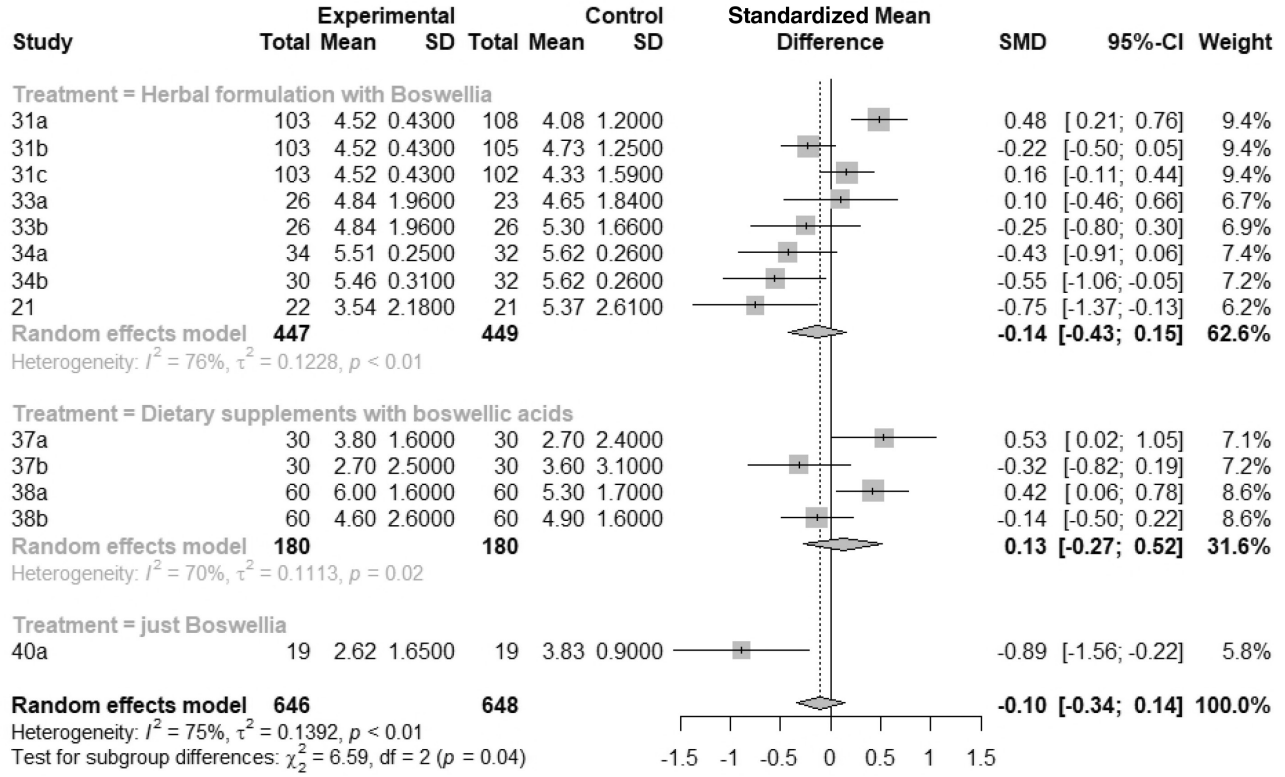

FIGURE 12 | Efficacy of *Boswellia* extracts in the management of knee OA: A forest plot of the VAS score subgroup analysis based on the treatment type.

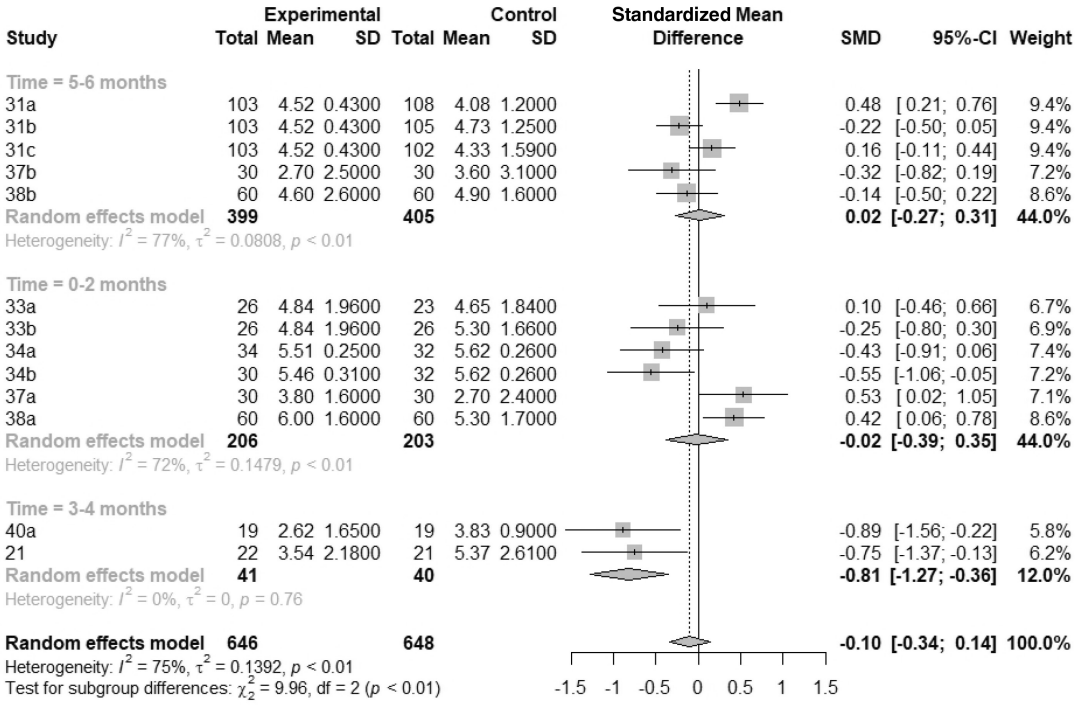

FIGURE 13 | Efficacy of *Boswellia* extracts in the management of knee OA: A forest plot of the VAS score subgroup analysis based on the duration of the studies.

A significant difference between the groups was detected ($p = 0.0069$). Of the studies that lasted 0–2 months, three data sets (33a, 33b, 34a) did not show significant differences between the control and the treatment groups, while 2 (37a, 38a) reported a higher VAS score in the treatment group, and the remaining one (34b) a lower score with respect to the control group. Only

the studies of Sengupta et al. (2010) and Sharkey et al. (2021) lasted 3–4 months and reported a significant difference between the control and the treatment groups, with the latter showing a lower VAS score, suggesting a beneficial effect of the supplementation. Despite the positive outcomes reported in studies lasting 3–4 months, of the five studies lasting 5–6 months, only one study showed significant differences between the groups, with a lower VAS in the positive control group (Chopra et al. 2013).

Of note, in the studies lasting 0–2 months (37a, 38a), Notarnicola et al. reported a significant difference in the treatment group which had a lower VAS score than the control group; however, at the last time point (5–6 months), no significant difference was detected (37b, 38b).

The studies lasting 0–2 and 5–6 months showed a very small effect size (SMD = −0.0183 and SMD = 0.0190, respectively), while the studies included in the 3–4 months group showed a large effect size (SMD = −0.8145).

3.8 | Meta-Regression Approach

To identify which factors had a significant influence on the meta-analysis effect size, meta-regression was carried out for the type of control, type of treatment, and time points for both the WOMAC and the VAS scores, respectively. The WOMAC score meta-regression outcome is reported in Figure S2.

The residual heterogeneity detected was 67.64% and R^2 was 67.29%; this percentage satisfactorily explained the I^2 residual. No significant association was detected concerning the time points and the different formulations used as supplements, suggesting that the duration of the study, the follow-ups, and different types of formulation with *Boswellia* (mixed with other extracts or used alone) did not influence the effect size. On the other hand, the use of a placebo as a control was significantly and positively associated with the outcome, indicating for the WOMAC score a higher effect size in comparison with negative control ($p = 0.0365$, estimate coefficient = 0.8168) or positive control ($p < 0.001$, estimate coefficient = 1.6282). Therefore, the meta-regression showed that the use of a placebo in the control group was associated with a significant decrease in the WOMAC score in the treatment group which received the supplementation with extracts of *Boswellia*. This could be of particular interest to those people who cannot tolerate the standard management (NSAIDS) due to concomitant pathologies.

By contrast, the outcomes obtained for the VAS score meta-regression detected a residual heterogeneity of 75.73%; however, the R^2 of 11.84% was too low to explain the substantial heterogeneity. Therefore, the results of the meta-regression of the VAS score did not show any significant association. The VAS score meta-regression outcome is reported in Figure S3.

4 | Limitations

On the market, there are different products to alleviate OA symptoms based on plant extracts with anti-inflammatory activities such as *C. longa*, *Z. officinalis*, *W. somnifera*, and *H. procumbens*. *Boswellia* extracts have been tested in different clinical studies often producing contradictory results due to differences in formulations, types of control, and finally, time points. Therefore, the meta-analysis was limited by the heterogeneity of the studies considered, but this weakness has been overcome using subgroup analysis and meta-regression. The authors also point out that WOMAC and VAS scores are self-reported questionnaires, although they are commonly accepted and encouraged in the evaluation of knee OA treatment.

Extracts of the oleogum resin obtained from the *Boswellia* genus have been used for centuries as a traditional treatment in Indian Ayurvedic medicine (Ammon 2016). Accordingly, the majority of the studies included in this meta-analysis were carried out in Eastern populations, with the exception of some studies carried out in Italy and the United States. This evidence could limit the generalization of the results obtained.

The variability and the insufficient characterization of the supplements deserved special attention. It is well known that *Boswellia* extracts show different compositions and quality, due to factors which include the use of different species of the genus *Boswellia*, different environmental conditions, and different extraction procedures. A prime example concerns the content of boswellic acids which is generally reported to be 65%. This value is often unrealistic as boswellic acids represent a percentage of the organic acids present in the phytoextract, the content of which is generally determined using unspecific titration methods that quantify all the organic acids present in the extract. This inconsistency is well known and has previously been highlighted by various authors (Bertocchi et al. 2018; Meins et al. 2016; Mannino, Occhipinti, and Maffei 2016).

Finally, the authors stress the fact that meta-analysis is a statistical and scientific technique that attempts to point out evidence in areas in which there are papers that report divergent outcomes. However, it cannot resolve a lack of evidence (Spector and Thompson 1991). The presence of possible effects deriving from not-measured or incompletely measured factors cannot be excluded. Moreover, as reported by Spector and Thompson (1991) publication bias and search bias are potential problems in all meta-analyses as unpublished studies may be in contrast with published results (Gurevitch et al. 2018).

5 | Strengths and Additional Research Needs

Recently, three meta-analyses on the efficacy of the use of *Boswellia* extracts on OA have been published. Yu et al. (2020) analyzed the effectiveness of *Boswellia* extracts for the treatment of OA in seven randomized controlled trials (Yu et al. 2020), while Bannuru et al. (2018) evaluated the effects of curcumin and *Boswellia*, and Smedslund et al. (2022) evaluated different available treatment options for OA, including the use of *Boswellia* extracts. This study represents an expansion from what Yu et al. (2020) reported as it included an analysis of 15 studies; in addition, unlike the other two studies, it is focused only on *Boswellia* extracts.

The strengths of the present meta-analysis are related to the inclusion of prospective studies with long-term follow-ups, up to

8 months, and the analysis of the possible sources of heterogeneity. In particular, the subgroup analysis and the meta-regression approach have clarified which factors, of those analyzed, were involved and could significantly change the effect size and, consequently, the outcomes of the studies.

Additional studies including a positive control and analyzing the possible effects of *Boswellia* alone or in combination with other phytoextracts are needed. Moreover, this meta-analysis showed a lack of studies carried out in Europe, with the exception of Italy.

6 | Conclusions

The anti-inflammatory activity of extracts from the oleogum resin of the *Boswellia* species has been addressed by many studies, including reviews, systematic reviews, and meta-analyses without, however, coming to any definitive conclusions regarding the actual efficacy of this phytoextract (Efferth and Oesch 2022; Yu et al. 2020; Smedslund et al. 2022). The present study provided additional evidence regarding the efficacy of extracts or bioactive molecules obtained from species of the *Boswellia* genus as CAM in knee OA management. In particular, the subgroup analysis demonstrated the significant beneficial effect of *Boswellia* extracts with respect to a placebo (lower WOMAC score in the treatment groups). This was also confirmed in the meta-regression applied to the WOMAC score. This is an important finding as people exposed to NSAID-related adverse effects could benefit from the use of *Boswellia* extracts.

However, data regarding the adverse effects and toxicity of these supplements are still incomplete, albeit extracts of *Boswellia spp.* have not exhibited toxicity in in vivo animal models (Di Lorenzo et al. 2013). There is a common sense that herbal products are safe while taking herbal remedies can be harmful and consumers are often not aware of their potential adverse effects (Dodda et al. 2022). Therefore, there is a discrepancy between the availability of these products on the market and the paucity of scientific information often characterized by poor methodology and unreliable clinical analysis (Furst and Zundorf 2015; Izzo et al. 2016). Further high-quality studies are needed to establish the clinical efficacy of *Boswellia* oleogum extracts.

Finally, another item worth to be considered is the chemical composition of supplements. The variability and the inaccurate supplement characterization deserve special attention, due to the lack of unbending guidelines regarding the safety and quality of phytoextracts; therefore, some marketed products might be absolutely ineffective. A formulation containing amounts of boswellic acids determined using a specific, accurate, and possibly standardized HPLC method is a prerequisite for evaluating any beneficial effects of a *Boswellia* extract.

Author Contributions

Thomas Dalmonte: conceptualization, data curation, formal analysis, methodology, software, writing – original draft. **Giulia Andreani:** resources, visualization. **Cecilia Rudelli:** data curation, investigation, visualization. **Gloria Isani:** conceptualization, methodology, project administration, resources, supervision, validation, writing – original draft.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data derived from public domain resources Data were obtained from references 30 to 42.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.