The Effectiveness and Application of *Urtica dioica* (Stinging Nettle) for Musculoskeletal Disorders: A Systematic Review and Meta-Analysis

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Abstract:

Musculoskeletal disorders (MSDs) are injuries of muscles, bones, tendons, joints, and ligaments commonly treated with medications like non-steroidal anti-inflammatory drugs and analgesic. However, undesired adverse effects with prolonged use have been reported. *Urtica dioica* (stinging nettle) has become one of the popular alternatives for MSDs as evident from literatures. This systematic review and meta-analysis were conducted to review the stinging nettle's effectiveness as well as formulations and methods of administration in the MSDs treatment. PubMed, Google Scholar, IIUM Online Library, CINAHL, and OVID were searched for studies from the earliest publication. Mean pain reduction scores included standard mean difference values as a principal outcome measure. The risk of bias and certainty of evidence were assessed based on the Cochrane Handbook Review and GRADEpro tool, respectively. Of seven studies included, the stinging nettle treatment was shown to effectively reduce the musculoskeletal pain with only minor adverse effects were reported (29%). Oral ingestion (57%) and polyherbal formulation (57%) were frequently used in stinging nettle applications. Probable synergistic effect from polyherbal formulation and no definitive effects determined from the single formulations. Hence, there is a need for carefully designed RCTs for stinging nettle preparations in the MSDs treatment to strengthen clinical relevance.

Keywords: musculoskeletal disorders (MSDs), musculoskeletal pain, effectiveness, safety, *Urtica dioica*, stinging nettle

Introduction:

Musculoskeletal disorders (MSDs), injuries of the human locomotor system covering bone, muscle, tendon, joint, and ligaments, is known for its debilitating effect globally (Middlesworth, 2019). In 2016, about 4.5% adults in Malaysia were living with MSDs (Jamaludin et al., 2018), many of whom were prescribed non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics. However, prolonged use of the drugs is found to be associated with undesired

adverse effects such as dizziness, constipation, and gastrointestinal (GI) effects (Babatunde et al., 2017).

Stinging nettle or *Urtica dioica* (family *Urticaceae*) is commonly known for its stinging hairs i.e. trichomes on its rough-textured leaves and stem. This perennial weedy plant is abundant in regions of the United States, North Africa, and parts of Asia (Baumgardner, 2016). It is shown to have anti-inflammatory and anti-rheumatic properties through the inhibition on nuclear factor kappa B, NF-kB activation, a transcription factor in the pro-inflammatory cytokines regulation, (Shakibaei et al., 2012; Farahpour & Khosgozaran, 2015) and analgesic characteristics (Safari et al., 2016). Due to these phytochemical properties, stinging nettle has become a popular alternative for MSDs (Hajhashemi & Klooshani, 2013). This was evidenced in The Lens database, where the patent and grant applications had risen dramatically from 2008 to 2015. This increasing trend, however, is slightly decreasing over the past few years and raising the question on the effectiveness of stinging nettle in treating MSDs. Therefore, this review aims to address the effectiveness of stinging nettle in the treatment of MSDs and its types of formulation and administration.

Methodology:

Search Strategies

This study was done based on the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines checklist (Moher et al., 2009). Google Scholar, PubMed, IIUM Online Library, CINAHL, and OVID were searched for articles from the earliest publication from 1987 to 2020 by using "stinging nettle" OR "*Urtica dioica*" OR "common nettle" AND osteoarthritis OR "musculoskeletal pain" OR "musculoskeletal disorders".

Original studies reporting on the effectiveness of stinging nettle tested on patients with MSDs related symptoms were included. Articles that defined the method of administration and formulation of stinging nettle were selected to fulfil the second objective of this study. The exclusion criteria included in-vitro and in-vivo studies related to stinging nettle, and duplicates, incomplete, or published articles in languages other than English.

Data Extraction and Collection

Data extracted were the first author's name, year of publication, number of patients, patients' characteristics, type of intervention, type of administration, formulation, and size of outcome variables as well as the funding sources when available (Ahn & Kang, 2018). The data extracted were recorded independently by two reviewers (SS and ZZ) using MS Excel 2019.

Data Analysis

The study was double-extracted and assessed for methodological appraisal by two reviewers (ZZ and NS) independently. Dichotomous data; ages and number of participants and the mean pain reduction scores including the outcome measures and outcome scale were collected from the searched articles. The quality assessment was done via a GRADEPro GDT evaluation tool (Schünemann et al., 2019).

Meta-Analysis

Random effect meta-analysis was used as the authors expected a heterogeneity but normally distributed data due to its broad scope of population and intervention (Deeks et al., 2019). The mean pain reduction scores were recorded with the standard mean difference (SMD) values i.e. effect size as a principal outcome measure. This effect size reflects the magnitude of the difference in outcomes between groups (Higgins & Green, 2011). By using Revman 5.3 software, the estimated effects of each study were pooled and presented in a forest plot at a 95% confidence level which the studies were evaluated for their overall effect size. The negative estimated values suggested the experimental effectiveness over the placebo tested.

Risk of Bias

Random sequence generation, allocation concealment, blinding of participants and personnel, and other domains were evaluated. Every study was graded to low, moderate or high risk or unclear (Higgins & Green, Chapter 7-8, 2011).

Results:

From 3,112 articles collected, seven articles met the eligibility criteria (Figure 1). The articles are two randomized controlled trials (RCTs) double-blind placebo-controlled (RCTs-PC), one RCT and one open-RCT, one RCT double-blind crossover (RCT-C), one open clinical trial, and one prospective case study. Two articles which had no placebo control group were excluded from the meta-analysis.

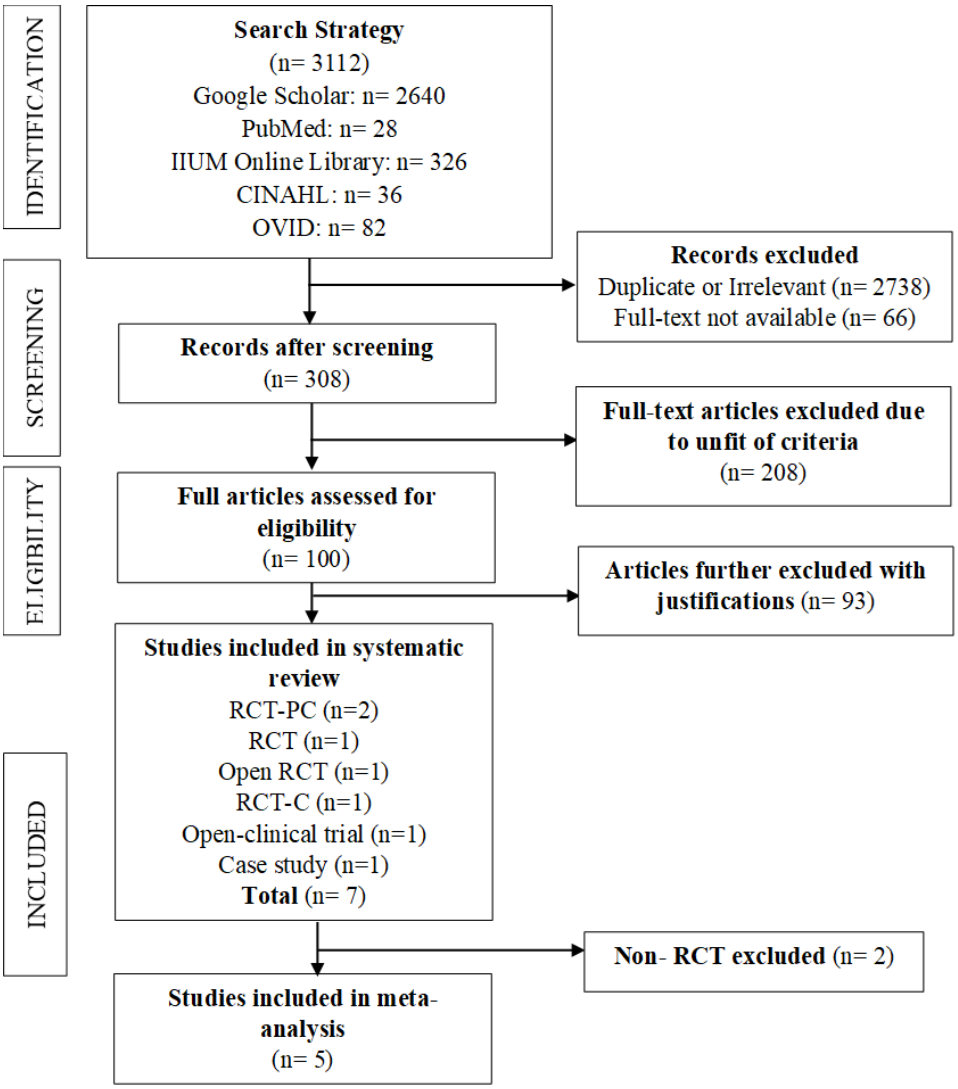

Figure 1 PRISMA flow diagram and search review process

Study Characteristics

Of the seven included studies, a total of four studies (57%) described polyherbal formulation in which two studies used mix herbs as the active ingredients and the other two used a combination of vitamins and herbs. Two studies used a higher amount of other herbs than that of stinging nettle. The oral use was demonstrated in four studies (57%), in capsules (43%) and blended (14%). The Visual Analogue Scale (VAS) score was mostly used for the authors main diagnosis (Hedaya, 2017; Randall et al., 2000). In addition to that, Moré et al. (2017), Jacquet et al. (2009), and Randall et al. (2008) employed the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score as their primary pain outcome measure. The secondary outcome measures in several studies applied were aligned to their respective objectives, though it is noted to be inconclusive for pain reduction outcome. All five out of seven studies implemented the placebo which almost akin to its experimental (treatment) study which is physical feature, color, odor, shape, taste, and texture. Other characteristics of the studies (herbal composition, dosage form, etc.) are summarized in Table 1.

Adverse Effects

Two studies (29%) reported mostly transient adverse effects which were easily resolved with or without treatment (Chrubasik et al., 1997) (Table 2). Out of 14 patients reported, one patient had withdrawn due to diarrhoea with positive rechallenge (Jacquet et al., 2015).

Table 1 Characteristics of included studies

Study and Setting	Subjects (♀/ ♂)	Design and Duration (mo)	Mean Age (SD), years old	Intervention type (name and composition)		Application of stinging nettle		Primary Outcome Measure	Secondary Outcome Measure	Diagnosis	NSAIDs/ Analgesic Usage	Funding Source
				Experimental (unit)	Control	Type of formulation	Type of administration					
Moré et al. (2017) Germany	90 (67/23)	RCT-PC (3)	MA212: 57.9 (8.3) CON: 55.7 (9.3)	MA212 (40ml/juice) [supplement] (formulation of *R. canina* [24g], *U. dioica* [0.160g dry leave extract], *H. zeyheri* [0.108g])	Vegetable juice mixture + olive oil + basil extract*	Polyherbal	Oral	WOMAC Pain Score	WOMAC scores (function/stiffness), pain diary (ASA, diclofenac)	Knee OA; 4-8 (Average WOMAC Pain Score)	No	MedAgil (mbH)
Hedaya (2017) USA	13 (8/5)	Case Study (0.5)	59.75 (88.26)	DrH RejointTM (0.35g/ capsule)[2 capsules twice per day] (blend of *U.dioica, B. serrata, E. arvense, A. satsativum, A. graveolans* [0.25g powder], vitamin B [0.02g])	Nil	Polyherbal	Oral	VAS Score	Nil	Over 18 y/o with persistent musculoskeletal pain; at least 4 months	No	Agency
Samal et al. (2015) India	50 (14/36)	Open Clinical Trial (1.5)	43.36 (11.07)	Ayush Harijawan Oil (2-3ml/oil) [twice per day] (formulation of *B. campestris*	Nil	Polyherbal	Topical	Modified Universal Pain Assessment Tool	Tenderness and swelling assessment tools	30-65 y/o; primary backache, knee and any	No	Agency

Study and Setting	Subjects (♀/ ♂)	Design and Duration (mo)	Mean Age (SD), years old	Intervention type (name and composition)		Application of stinging nettle		Primary Outcome Measure	Secondary Outcome Measure	Diagnosis	NSAIDs/ Analgesic Usage	Funding Source
				Experimental (unit)	Control	Type of formulation	Type of administration					
				[0.53g], *E. globulus* [0.05g], *C. camphora* [0.11g], *U. dioica* [0.11g], *A. sativum* [0.11g], *M. fragrans* [0.05g], *P. nigrum* [0.05g])						muscular pain		
Jacquet et al. (2009) France	81 (55/26)	RCT-PC (3)	Phytalgic®: 56.8 (3.04) CON: 57.5 (13.07)	Phytalgic® (0.1g/capsule) [3 capsules per day] (formulation of *U. dioica* [0.06g], zinc [0.01g], vitamin C&E [0.012g], and omega-3 fatty acids)	Capsules (non-fish oils without omega-3 /omega-6 fatty acids)	Polyherbal	Oral	WOMAC Score	Patient diary (0.5g paracetamol or 0.2g ibuprofen per week and NSAIDs [DDD], slow-acting drugs [DDD/day]	40-80 y/o; chronic knee or hip OA; NSAIDs-dependents for pain relief	Yes**	Phythea Laboratories
Randall et al. (2008) United Kingdom	42 (18/24)	RCT (2)	Nettle sting: 65 (7.2), CON: 67 (6.5)	Nettle sting [once daily for 7 days] (*U. dioica* fresh leaves)	Non-stinging' nettle (*U. Galeopsifolia* ***)	Single	Topical (leaves of both groups were pressed on the painful knee for 10 seconds and repeated twice on the other sides)	WOMAC Pain Subscale Score	VAS Score, WOMAC B/C, Pain diary, Nurse Attendance	55-80 y/o; Knee OA (ACR clinical criteria)	No	South West General Practice Trust

Study and Setting	Subjects (♀/ ♂)	Design and Duration (mo)	Mean Age (SD), years old	Intervention type (name and composition)		Application of stinging nettle		Primary Outcome Measure	Secondary Outcome Measure	Diagnosis	NSAIDs/ Analgesic Usage	Funding Source
				Experimental (unit)	Control	Type of formulation	Type of administration					
Randall et al. (2000) United Kingdom	27(23/4)	RCT-C (3) 5 weeks of washout period between 2 experimental weeks	61.75(57.5)	*U. dioica* plant	Non-stinging placebo (*L. album* plant***)	Single	Topical (base of thumb pain of OA)	VAS Score	VRS Score, use of analgesics, sleep analogue VAS score, Side effects and patient comments	Over 18 y/o; persistent base thumb or index finger OA of at least 10 weeks	No	Self-sponsor
Chrubasik et al. (1997) Germany	36 (18/18)	Open-RCT (0.5)	Stewed *U. dioica*: 52 (20.0) CON: 63 (15.5)	Young leaves *U. dioica* [25g per week] (with 0.05g diclofenac)	Diclofenac [0.1g per week] (with misoprostol)	Single	Oral	The relative improvement of elevated C-reactive protein serum	VRS Score (total joint scores, subjective pain and pain on pressure, and stiffness)	Acute arthritis (no suffering from severe hepatic or renal disease); 3 weeks	Yes (diclofenac)	Self-sponsor

SD= standard deviation, CON= control, WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index scale, VAS= Visual Analogue scale, VRS= Verbal Rating scale, OA= osteoarthritis

*Not specified, ** to assess both treatment and control effect on the medication with prior hypothesis that the treatment would decrease the symptoms and reduce the usage of analgesics by at least 20% from initial stage (Jacquet et al., 2015), ***phenotypically similar to *U. dioica*

Table 1 Reported adverse effects from two studies

Study	No. of patients	Events***
Jacquet et al. (2015)	EXP: 14	1,2,3,4
	CON: 13	1,5,6,7,8,9
Chrubasik et al. (1997)	EXP: 3	1,10
	CON: 3	11

EXP= Experimental, CON= Control

***1, diarrhoea; 2, eructation smelling of fish-oil; 3, pain at sciatic, lumbar, scapula and dental; 4, common cold, lymphangitis; 5, gastroenteritis; 6, hypercholesterolaemia; 7,dental problems; 8, cystitis; 9, vomiting and GI pain; 10, abdominal pain; 11, meteorism.

Risk of Bias

Four RCTs adequately fulfilled all domains (Moré et al., 2017; Jacquet et al., 2009; Randall et al., 2008; Randall et al., 2000). This includes low risk in allocation concealment by means of of computerized random generator, identical capsules (both treatment and placebo), serially numbered, and opaque bags. However, two studies had a high risk of bias (Samal et al., 2015; Hedaya, 2017) and one for high risk of confounding bias and sequence generation (Chrubasik et al., 1997) (Table 3)

Table 2 Risk of bias assessment on the included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Moré et al. (2017)	L	L	L	L	L	L	L
Hedaya (2017)	H	H	U	U	L	L	L
Samal et al. (2015)	H	H	H	H	L	L	L
Jacquet et al. (2009)	L	L	L	L	L	L	L
Randall et al. (2008)	L	L	L	L	L	L	L
Randall et al. (2000)	L	L	L	L	L	L	L
Chrubasik et al. (1997)	H	L	H	M	U	U	H

L= Low risk, U= Unclear, H= High risk, M= Moderate risk

Effectiveness of Stinging Nettle (and Quality Evidences)

The meta-analysis indicated no significant difference with negative pooled estimate effect of -0.53 (95% CI -2.35 to 1.29, p = 0.57) between the experimental and control groups (Figure 2). Despite the considerable heterogeneity i^2 = 98% with a wide confidence interval (CI), the experimental effect was shown consistent among the studies given small prediction interval effect (95% prediction interval -0.85 to -0.21). The high credible evidences (Table 4): Randall et al. (2000) and Jacquet et al. (2009) exerted statistically significant large effects -4.23 (95% CI -5.22 to -3.24, p < 0.001) and -1.26 (95% CI -1.73 to -0.78, p < 0.001), respectively. Randall et al. (2008) with their placebo, *U. Galeopsifolia* was found to demonstrate small treatment effect from imprecision 0.04 (95% CI -0.57 to 0.64) (as indicated by a wide CI). Chrubasik et al. (1997) also revealed small true effect from imprecision 0.20 (95% CI -0.46 to 0.85). While, Moré et al. (2017) was found to favor the placebo instead with 2.47 (95% CI 1.92 to 3.02, p < 0.001). Other two studies indicated small effect sizes as referred in Table 5.

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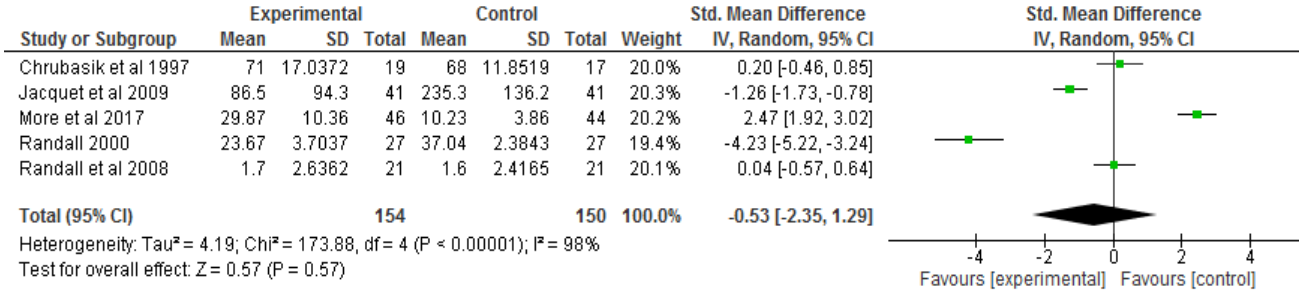

Figure 2 Random effect meta-analysis of five studies that determine the effectiveness of stinging nettle (experimental) on MSDs patients

Discussion:

The true effects were observed substantial with imprecision in several studies (Randall et al., 2008; Chrubasik et al., 1997) emphasizing the need for large studies with large effects as seen in Randall et al. (2000) and Jacquet et al. (2009). This explains the impact of a small study through its result of a wide CI and small effect size. Samal et al. (2015) and Hedaya (2017), two of which exempted from meta-analysis were analyzed based on the estimated effect sizes cohen's *d*. The small studies presented too small an effect to be considered as clinically meaningful despite the significant effects reported (Table 5). The overall results are pooled for SMD via the random effect meta-analysis as the different scales of outcome measure. SMD converted data from different scales to common scale. When the 95% prediction interval was calculated, the negative pooled estimate effect -0.53 (95% CI -2.35 to 1.29, $p = 0.57$) showed significance given the small interval (95% prediction interval -0.85 to -0.21). The consistency was demonstrated, $p = 0.57$ (p-value > 0.05) which exhibits a higher probability for clinical effectiveness of stinging nettle in MSDs.

The possible mechanisms of stinging nettle actions are via its derivative of phytochemicals i.e. flavonoids, tannins, and phenolic acids (Said et al., 2015; Yousef et al., 2015). These phytochemicals have an anti-inflammation effect, demonstrating the stabilization of NF-kB complex activation on the IL-1β-induced human canine articular chondrocytes (Shakibaei et al., 2012). The pain reduction from the anti-inflammation of stinging nettle is further documented by Hajhashemi and Klooshani (2013). Safari et al. (2016) also found peripheral analgesic activity from the nettle leaf administration on pain-induced mice. However, the exact mechanism of the said effectiveness of the plant remains elusive.

The indirect effect of stinging nettle from polyherbal formulation lies in the herb-herb combinations concept that have been shown to produce potential interaction effects including mutual enhancement and assistance producing synergistic effect (Sun et al., 2019). However, we do acknowledge that only little effect could be attributed to the lower content of stinging nettle as as compared to the other mixed herbs in the two studies This differs from the single formulation studies, where the effectiveness of stinging nettle may have illustrated by the positive interactions between the active phytochemicals responsible like flavonoids, tannins, and other constituents of hydroethanolic extract for anti-inflammation and analgesic properties (Sun et al., 2019).

Table 3 GRADE of quality evidences

	Certainty assessment						Certainty
№	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Absolute (95% CI)	
1 Moré et al. (2017)	not serious	not serious	not serious	not serious	none	SMD 2.47 SD higher (1.92 higher to 3.02 higher)	⨁⨁⨁⨁ HIGH
1 Hedaya (2017)	serious [a]	not serious	not serious	not serious	strong association	MD 34.71 SD lower 18.13	⨁⨁⨁◯ MODERATE
1 Samal et al. (2015)	serious [a]	not serious	not serious	not serious	none	MD 1.4 SD lower 0.75	⨁◯◯◯ VERY LOW
1 Jacquet et al. (2009)	not serious	not serious	not serious	not serious	very strong association	SMD 1.26 SD lower (1.73 lower to 0.78 lower)	⨁⨁⨁⨁ HIGH
1 Randall et al. (2008)	not serious	not serious	not serious	serious [c]	none	SMD 0.04 SD higher (0.57 lower to 0.64 higher)	⨁⨁⨁◯ MODERATE
1 Randall et al. (2000)	not serious	not serious	not serious	not serious	strong association	SMD 4.23 SD lower (5.22 lower to 3.24 lower)	⨁⨁⨁⨁ HIGH
1 Chrubasik et al. (1997)	very serious [b]	not serious	not serious	serious [c]	residual confounding[d]	SMD 0.2 SD higher (0.46 lower to 0.85 higher)	⨁⨁◯◯ LOW

EXP: experimental, CON: control, CI: confidence interval, SD: standard deviation, MD: mean difference, SMD: standardized mean difference

[a] Non-blinding and lack of randomized and control group.

[b] **S**ignificant confounders; age and origin of pain in both groups and performance bias

[c] Wide CI

[d] Plausible residual confounding would suggest spurious effect, while no effect was observed

Table 4 Mean difference of pain scores and effect sizes of two studies excluded from the meta-analysis

Study	Mean difference of pain scores (SD)	Effect Size Cohen's *d* (95% CI)
Hedaya (2017)	0.34 (0.19)	1.79 (0.26, 0.47)
Samal et al. (2015)	2.00 (2.52)	0.79 (1.04, 2.95)

The high prevalence of oral use may reflect the most convenient method of drug delivery with high patient compliance (Savjani et al., 2012). Nevertheless, it requires an "upgrade" of the oral drug for significant manifestation of its pharmacological effects (Savjani et al., 2012) based on its low bioavailability

from pre-systemic metabolism and the drug biotransformation that occurs along the GI tract (Latifa et al., 2007). This can be seen in a study by Chrubasik et al. (1997) that uses capsules prepared with isolated compounds using a high-performance liquid chromatography, HPLC for standard calibration. The particle size reduction in MA212 by Moré et al. (2017) improve its solubility and gastric emptying rate (Savjani et al., 2012). The topical applications of stinging nettle, either in the form of oil (Samal et al., 20015) or leaves (Randall et al., 2008; Randall et al., 2000), provide localized effect and confer prolonged drug release due to longer plasma half-life than oral ingestion (Jalloh, 2016) .Besides the above-mentioned factors, other aspects like age, gender, and disease severity can also affect the oral bioavailability and maximum plasma drug concentration which may lead to discrepancies in the therapeutic effects (Jalloh, 2016).

A considerable heterogeneity between the selected studies were probably due to different interventions and outcome measures which might explain the non-significant difference in the pooled estimate effect. The existence of heterogeneity were managed by using a random-effect model and 95% prediction interval to determine the overall interval effect. The small placebo effects in Moré et al. (2017) may complicate the result interpretation. While, few studies demonstrated significant imprecision (Randall et al., 2008; Chrubasik et al., 1997) and confounding bias of Chrubasik et al. (1997) which degrade the certainties of evidence. This warrants future RCTs of standardized stinging nettle preparation to assess its effectiveness and safety.

Conclusion:

The findings of this original article provide a concise overview and support of the stinging nettle effectiveness in MSDs due to consistent treatment effectiveness demonstrated with minor adverse effects. Of note, the stinging nettle is commonly taken orally in the form of capsules and blends, and polyherbal formulated. However, larger RCTs are warranted for higher reliability. Therefore, until further evidence is available, the use of stinging nettle should be considered as an alternative therapy to NSAIDs and analgesics in the treatment of MSDs.

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Author Contributions

SSAZ wrote the main body of the paper. ZZ and NS provided feedback on the draft paper and approved the drafted manuscript. All authors read and approved the final manuscript.

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