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REVIEW

Antioxidant and anti-inflammatory dietary supplements in the treatment of osteoarthritis: a scoping review

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Abstract

The increasing number of evidence has reported inflammation and oxidative stress as key mediators of osteoarthritis (OA) joint pathology. Therefore, the usage of dietary supplements targeting inflammation and oxidative stress in OA may emerge as a rewarding therapeutic strategy. This study aimed to explore the efficacy of antioxidant and anti-inflammatory dietary supplements used to manage OA. A methodological framework proposed by Arksey and O'Malley was used to conduct this scoping review. An electronic database search of English academic articles was conducted using PubMed, MEDLINE and ScienceDirect from 2000 to 2018. Randomized controlled trials (RCTs) of OA with parallel groups by comparing dietary supplements with placebo consumption were eligible for inclusion. Out of 69,150 studies identified, a total of 41 studies were included, with 25 antioxidant or anti-inflammatory dietary supplements identified. There were 3325 respondents (1740 in the treatment group and 1585 in the placebo group), all aged ≥ 25 years old and comprised of 69.6% and 30.4% female and male respondents, respectively. The majority of the studies recruited participants with knee OA (n = 33) with a follow-up duration of 3 to 32 weeks. Overall, most of the dietary supplements (n =17) demonstrated a beneficial effect on the clinical signs and symptoms, such as Boswellia serrata extract (BSE), Pycnogenol and L-carnitine. In contrast, Aquamin supplementation did not exert positive impacts on OA management, while inconsistent findings were observed in green-lipped mussel (GLM) extract, vitamin E, methylsulfonylmethane (MSM), licorice flavonoid oil (LFO), ginger, willow bark extract and rose hip supplementation. In summary, the role of anti-inflammatory and antioxidant dietary supplements cannot be ignored as they can offer alleviated pain and symptom relief.

1. Introduction

Osteoarthritis (OA) is a progressive joint disease that is attributed to a biochemical or genetic factor (Ministry of Health, 2013). OA is characterized by the degeneration and loss of articular cartilage accompanying the synovial inflammation, which is associated with pain (Doherty *et al*., 2016). It is the most prevalent form of arthritis (Bijlsma *et al.,* 2011) and a major cause of disability worldwide (Conaghan *et al.*, 2014). It can occur in various joints, such as hip, knee and hand, whereby knee osteoarthritis (KOA) is more common (Zhang and Jordan, 2010).

The incidence of OA is becoming more prevalent due to the increasing number of elderly and obesity cases (Neogi and Zhang, 2013; Nur Aimi *et al.,* 2018). It is expected that OA will contribute to an increased burden due to the aging population and unhealthy lifestyle (Belcaro *et al*., 2008b). According to Woolf and Pfleger (2003), 9.6% of men and 18.0% of women aged over 60 years have symptomatic OA, with 25.0% of them being unable to carry out routine daily activities.

Recently, the use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) as the first-line medication has been questioned due to their adverse side effects, such as increased risk of peptic ulcers and upper gastrointestinal bleeding (da Costa *et al*., 2017). Thus, this prompts the patients to find alternative treatments, with dietary supplements or non-pharmacological supplements usage emerging as a complementary or alternative treatment for OA patients (Green *et al.*, 2014).

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OA is no longer viewed as a mere wear-and-tear problem (Rosenbaum *et al*., 2010). On the contrary, there is increasing evidence highlighting inflammation and oxidative stress as the key mediators of OA joint pathology, suggesting the use of dietary supplements targeting these elements in OA to be a potentially rewarding therapeutic strategy (Philp *et al.,* 2016). Hence, this review aimed to explore further on the efficacy of antioxidant and anti-inflammatory dietary supplements used to manage OA.

2. Materials and method

The present study was designed as a scoping review, which investigated the efficacy of antioxidant and anti-inflammatory dietary supplements used to manage OA. The five-stage methodological framework outlined by Arksey and O'Malley (2005) was used as a guideline for the scoping review, which consisted of: (1) identifying the research questions; (2) identifying the relevant studies; (3) selecting studies; (4) charting the data; and (5) collating, summarizing and reporting the results. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram illustrated the flow of articles from the search to its final selection as shown in Figure 1 (Moher *et al.,* 2009).

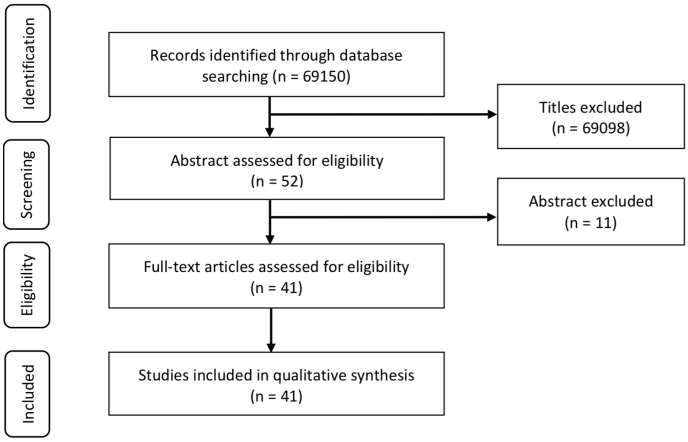

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of study selection

2.1 Identifying the research questions

The review questions were: (1) what types of antioxidant and anti-inflammatory dietary supplements and their active ingredients are used among OA patients?; and (2) what is the efficacy of antioxidant and anti-inflammatory dietary supplements used to manage OA?

2.2 Identifying relevant studies

Academic journals (English) published from 2000 to 2018 were identified by conducting electronic databases search using PubMed, MEDLINE and ScienceDirect. All RCTs with parallel groups, excluding systematic reviews or review papers, were included in the search. Titles, abstracts and keywords were examined independently for eligibility by the researchers. A total of 41 studies were included in this review from 69,150 studies identified through the electronic databases search. Key search terms used to search the articles are displayed in Table 1 below.

Table 1. Key search terms in the scoping review

Antioxidant OR Anti-inflammatory supplements AND
Dietary supplements OR Nutraceuticals AND Osteoarthritis
Omega-3 fatty acids OR Fish oil AND Osteoarthritis
Krill Oil AND Osteoarthritis
Green-lipped mussel extract OR Perna canaliculus AND Osteoarthritis
Vitamin E OR Tocopherol OR Tocotrienol AND Osteoarthritis
Willow bark extract AND Osteoarthritis
Methylsulfonylmethane AND Osteoarthritis
Avocado/soybean unsaponifiables AND Osteoarthritis
Boswellia serrata extract OR Aflapin OR 5-Loxin AND Osteoarthritis
Pine bark extract OR Pycnogenol AND Osteoarthritis
Vitamin C OR Ascorbic acid AND Osteoarthritis
L-carnitine AND Osteoarthritis
Artemisia annua extract AND Osteoarthritis
Deer bone extract AND Osteoarthritis
Garlic Or Allium sativum AND Osteoarthritis
Bitter Melon Or Momordica charantia AND Osteoarthritis
Argan oil AND Osteoarthritis
Liquorice flavonoid oil AND Osteoarthritis
Ginger OR Zingiber officinale AND Osteoarthritis
Pomegranate AND Osteoarthritis
Sesame seed AND Osteoarthritis
Russian olive AND Osteoarthritis Phytalgic AND Osteoarthritis
Calcium fructoborate AND Osteoarthritis
Aquamin AND Osteoarthritis
Soy protein AND Osteoarthritis
Rose hip AND Osteoarthritis
Turmeric or Curcumin AND Osteoarthritis
Beta-carotene OR Vitamin A AND Osteoarthritis
Purple passion fruit peel extract AND Osteoarthritis

2.3 Selecting studies

Studies were eligible for inclusion in this review should they meet the following inclusion criteria: (1) patients diagnosed with OA and had not undergone surgery; (2) reported outcomes, such as pain, physical function, stiffness, quality of life, and pain medication usage; and (3) evaluated the efficacy of individual dietary supplements.

2.4 Charting the data

The data presented were author(s), year of publication, country, study design, types of supplement and its active ingredients, participants' characteristics, outcomes reported, and results displayed in mean ± standard deviation and p-value, which were relevant to

the review.

2.5 Collating, summarizing and reporting the results

Findings of the review on the efficacy of antioxidant and anti-inflammatory dietary supplements used to manage OA were presented.

3. Results

3.1 Study characteristics

From the 41 studies included, a total of 25 antioxidant or anti-inflammatory dietary supplements were identified. The research evidence on the efficacy of these dietary supplements is summarized in Supplementary Table 2. The total number of respondents were 3325 (1740 in the treatment group and 1585 in the placebo group), all of which aged ≥ 25 years old. There were more female participants compared to male (69.6%:30.4%). Patients' population in studies done by Dehghani *et al.* (2018), Malek Mahdavi, Mahdavi, and Kolahi (2016), Malek Mahdavi *et al.* (2015) and Salimzadeh *et al*. (2018) included only females. Only one study did not provide information regarding the gender sampled (Eftekhar Sadat *et al.,* 2013). The majority of the studies recruited participants with knee OA (n = 33). Meanwhile, six studies involved participants with either knee or hip OA (Schmid *et al*., 2001; Warholm *et al*., 2003; Jacquet *et al*., 2009; Ginnerup-Nielsen *et al*., 2015; Hunt *et al.,* 2016; Stebbings *et al*., 2017), whereas three studies did not state the affected OA region (Belcaro *et al.*, 2008a; Belcaro *et al.*, 2010). The follow-up duration for the included studies ranged from 3 to 32 weeks. The follow-up duration was classified into three categories, namely short term (≤ 12 weeks), medium term (12 to 24 weeks), and long term (> 24 weeks) (Liu *et al*., 2018). Most of the studies were conducted within a short term duration (n = 35), while five studies followed up in the medium term duration (Brand *et al*., 2001; Warholm *et al.,* 2003; Lau *et al*., 2004; Srivastava *et al*., 2016; Kinoshita *et al*., 2017) and only one study followed up in the long term duration (Gianni Belcaro *et al*., 2010).

Eight studies were conducted in European countries (Appelboom *et al.*, 2001; Schmid *et al.,* 2001; Warholm *et al.*, 2003; Cisár *et al.*, 2008; Belcaro *et al.*, 2008a; Jacquet *et al.,* 2009; Belcaro *et al*., 2010; Ginnerup-Nielsen *et al*., 2015), five studies in the United States of America (Altman and Marcussen, 2001; Arjmandi *et al*., 2004; Kim *et al.*, 2006; Frestedt *et al.*, 2009; Pietrzkowski *et al*., 2014), four in Oceanian countries (Brand *et al*., 2001; Farid *et al.*, 2010; Hunt *et al.*, 2016; Stebbings *et al.,* 2017) and one study conducted in Africa country (Essouiri *et al.,* 2017). The remaining 23 studies were conducted in Asian countries. All of the studies included were single-center double-blind RCTs, excluding one study of single-center single-blind RCT (Lim *et al.,* 2018), one study of multicenter double-blind RCT (Altman and Marcussen, 2001), two studies of single-center double-blind prospective study (Debbi *et al.*, 2011; Nakagawa *et al*., 2014), and two multicenter double-blind prospective studies (Appelboom *et al.,* 2001).

3.2 Dietary supplements with positive results

Overall, out of 25 dietary supplements identified, 17 of them demonstrated beneficial effect on clinical signs and symptoms. These dietary supplements were krill oil (Suzuki *et al.,* 2016), avocado/soybean unsaponifiables (ASU) (Appelboom *et al.,* 2001), curcumin (Gianni Belcaro *et al.,* 2010; Nakagawa *et al.,* 2014; Panahi *et al.,* 2014; Srivastava *et al.,* 2016), BSE (Sengupta *et al*., 2008; Sengupta *et al*., 2010; Vishal *et al.,* 2011), Pycnogenol (Belcaro *et al*., 2008a; Cisár *et al.*, 2008; Farid *et al*., 2007), purple fruit passion peel (PFP) extract (Farid *et al.,* 2010), L-carnitine (Malek Mahdavi *et al*., 2015; Malek Mahdavi, Mahdavi and Kolahi, 2016), Artemisia annua (ART) extract (Hunt *et al.*, 2016), deer bone extract (DBE) (Shin *et al*., 2018), garlic (Dehghani *et al.,* 2018; Salimzadeh *et al.,* 2018), Momordica charantia (Lim *et al.*, 2018), argan oil (Essouiri *et al*., 2017) pomegranate juice (PJ) (Ghoochani *et al.*, 2016), sesame seed (Eftekhar Sadat *et al*., 2013), Phytalgic® (Jacquet *et al*., 2009), soy protein (Arjmandi *et al.*, 2004) and calcium fructoborate (CFB) (Pietrzkowski *et al*., 2014).

3.3 Dietary supplements with negative results

Frestedt *et al.* (2009) reported that Aquamin supplementation is ineffective in symptoms of improvement among OA patients.

3.4 Dietary supplements with mixed results

Inconsistent findings were observed in GLM extracts (Lau *et al*., 2004; Stebbings *et al.*, 2017), vitamin E (Brand *et al.,* 2001; Tantavisut *et al.*, 2017), MSM (Kim *et al*., 2006; Debbi *et al*., 2011), rose hip (Warholm *et al.*, 2003; Ginnerup-Nielsen *et al*., 2015), LFO (Kinoshita *et al.*, 2017), ginger (Alipour *et al.*, 2016; Altman and Marcussen, 2001; Niempoog *et al.*, 2012; Zakeri *et al.,* 2011) and willow bark extract (Schmid *et al*., 2001).

4. Discussion

Recent evidence suggested that inflammation (Lei *et al.*, 2017) and oxidative stress (Chin and Ima-Nirwana, 2018) are involved in the underlying mechanism leading to the cartilage degradation in OA. Not surprisingly, OA

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Table 2. Summary of RCTs of antioxidant and anti-inflammatory dietary supplements for the treatment of OA

Supplements (Bioactive compounds)	Author, year	Country	Study design	Participants characteristics (n, gender, age, OA region affected)	Dosage regime, duration	Outcomes reported	*M*±*SD*, p-value: Treatment group (T0-T1)	Placebo group (P0-P1)	Treatment-Placebo (TI-P1)
Krill oil (EPA and DHA)	Suzuki *et al.* (2016)	Japan	Double-blind	**T** n = 25 (4M/21F), age = 65.8±10.1 **P** n = 22 (2M/20F), age = 63.6±10.9 OA region affected = knee	**T** (2 g/d) vs **P**, 30 days	JKOM total scores	**T0** = 43.6±11.1 **T1** = 33.5±7.82 $p = 0.000$*	**P0** = 45.6±11.8, **P1** = 38.0±15.1 $p = 0.016$*	$p = 0.223$
GLM extract (EPA and DHA)	Stebbings *et al.* (2017)	New Zealand	Double-blind	**T** n = 39 (17M/22F), age = 66.5±10.8 **P** n = 41 (19M, 22F), age = 66.3±9.3 OA region affected = knee or hip	**T** (600 mg/d) vs **P**, 12 weeks	Pain VAS	**T0** = 5.3±2.1 **T1** = 5.0±2.8	**P0** = 4.5±2.1 **P1** = 4.6±2.3	$p = 0.110$
						WOMAC stiffness scores	**T0** = 3.5±1.6 **T1** = 3.0±1.6	**P0** = 3.9±1.4, **P1** = 3.7±1.4	$p = 0.046$*
						Paracetamol use	-	-	$p = 0.045$*
GLM extract (EPA and DHA)	Lau *et al.* (2004)	China	Double-blind	**T** n = 40 (5M/35F), age = 62.18 (47-74) **P** n = 40 (6M, 34F), age = 62.9 (46-80) OA region affected = knee	**T** (4 capsules/d) vs **P**, 6 months	Pain VAS	**T0** = 63.0±14.3 **T1** = 54.0±15.2 *$p = 0.042$**	**P0** = 66.2±15.7 **P1** = 67.1±5.5 *$p > 0.05$*	$p = 0.045$*
Vitamin E (α-tocopherol)	Tantavisut *et al.* (2017)	Thailand	Double-blind	**T** n = 31 (2M/29F), age = 69.50±1.30 **P** n = 35 (9M, 26F), age = 69.20±1.30 OA region affected = knee	**T** (400 IU/d) vs **P**, 2 months before surgery	WOMAC scores:			
						Pain	**T0** = 23.8±1.69, **T1** = 19.2±1.43	**P0** = 25.2±1.19, **P1** = 27.3±0.89	$p < 0.001$*
						Stiffness	**T0** = 8.94±1.02, **T1** = 5.45±0.73	**P0** = 7.80±0.87, **P1** = 8.23±0.79	$p = 0.01$*
						Physical function	**T0** = 90.6±7.12, **T1** = 72.7±6.55	**P0** = 90.1±4.72, **P1** = 94.8±4.22	$p < 0.001$*
	Brand *et al.* (2001)	Australia	Double-blind	**T** n = 39 (16M/23F), age = 67.1±1.4 **P** n = 38 (16M, 22F), age = 66.1±1.5 OA region affected = knee	**T** (500 IU/d) vs **P**, 6 months	WOMAC scores:			
						Pain	**T0** = 49.2, **T1** = 71.5 $p > 0.05$	**P0** = 61.7, **P1** = 66.7 $p > 0.05$	$p = 0.59$
						Stiffness	**T0** = 25.7, **T1** = 34.1 $p > 0.05$	**P0** = 28.8, **P1** = 33.6 $p > 0.05$	$p = 0.92$
						Function	**T0** = 209, **T1** = 280 $p > 0.05$	**P0** = 242, **P1** = 279. $p > 0.05$	$p = 0.99$
MSM (organic sulfur compound)	Debbi *et al.* (2011)	Israel	Prospective, double-blind	**T** n = 25 (4M/21F), age = 67.0±9.8 **P** n = 25 (13M, 12F), age = 71.0±8.3 OA region affected = knee	**T** (3.375 g/d) vs **P**, 12 weeks	WOMAC total scores:	**T0** = 40.9±20.3, **T1** = 33.3±22.5	**P0** = 47.0±22.2, **P1** = 53.5±20.3	$p = 0.03$*
						VAS pain score	**T0** = 3.78±3.04, **T1** = 3.61±2.9	**P0** = 4.60±2.74, **P1** = 5.16±2.22	$p = 0.05$*

Table 2. Summary of RCTs of antioxidant and anti-inflammatory dietary supplements for the treatment of OA (Cont.)

Supplements (Bioactive compounds)	Author, year	Country	Study design	Participants characteristics (n, gender, age, OA region affected)	Dosage regime, duration	Outcomes reported	*M*±*SD*, p-value: Treatment group (T0-T1)	Placebo group (P0-P1)	Treatment-Placebo (TI-P1)
MSM (organic sulfur compound)	Kim *et al.* *(2006)*	USA	Double-blind	**T** n = 21 (9M/12F), age = 56.6±8.6 **P** n = 19 (6M, 13F), age = 55.6±8.7 OA region affected = knee	**T** (6 mg/d) vs **P**, 12 weeks	WOMAC scores:			
						Pain	**T0** = 58.0±5.5 **T1** = 43.4±4.6	**P0** = 55.1±5.8 **P1** = 47.9±4.8	$p = 0.041$*
						Physical function	**T0** = 51.5±4.5 **T1** = 35.8±3.2	**P0** = 52.9±5.9 **P1** = 44.1±5.1	$p = 0.045$*
ASU (Phytosterols β-sitosterol, campesterol, and stigmasterol)	Appelboom *et al.* (2001)	Belgium	Prospective, multicenter double blind	**TI** n = 86 (19M/67F), age = 63.4±8.6 **TII** n = 86 (21M/65F), age = 65.2±8.5 **P** n = 88 (15M, 73F), age = 66.3±8.1 OA region affected = knee	**TI** (300 mg/d) or **TII** (600 mg/d) vs **P**, 3 months	NSAIDs and analgesics intake	**TI0** = 143±47.8 **TI1** = 45.2±51.7 **TII0** = 130.7±51.5 **TII1** = 52.5±59.2	**P0** = 136±54.7 **P1** = 81.0±63.4	$p < 0.01$* (P1 compared to TI1 and TII1)
						VAS pain score	**TI0** = 57.8±13.1 **TI1** = 24.2±21.2 **TII0** = 55.1±11.8 **TII1** = 28.3±20.8	**P0** = 53.7±12.6 **P1** = 42.4±21.4	$p < 0.01$* (P1 compared to TI1 and TII1)
Curcuma longa L. (CL) (Curcumin)	Srivastava *et al.* (2016)	India	Double-blind	**T** n = 78 (25M/53F), age = 50.23±8.08 **P** n = 82 (32M, 50F), age = 50.27±8.63 OA region affected = knee	**T** (1000 mg/d) vs **P**, 4 months	WOMAC scores:			
						Pain	**T0** = 15.10±0.31 **T1** = 9.48±0.17	**P0** = 15.3±0.26 **P1** = 10.2±0.16	$p = 0.01$*
						Physical function	**T0** = 54.0±0.68 **T1** = 32.1±0.40	**P0** = 51.0±0.68 **P1** = 33.9±0.50	$p = 0.008$*
						VAS pain score	**T0** = 7.94±0.13 **T1** = 4.03±0.08	**P0** = 7.66±0.14, **P1** = 5.11±0.14	$p = 0.000$*
Theracurmin (Curcumin)	Nakagawa *et al.* (2014)	Japan	Double-blind, prospective	**T** n = 18 (4M/18F), age = 71.9±5.3 **P** n = 23 (5M, 23F), age = 66.1±7.2 OA region affected = knee	**T** (180 mg/d) vs **P**, 8 weeks	VAS pain score	**T0** = 0.60 **T1** = 0.20	**P0** = 0.47 **P1** = 0.23	$p = 0023$* (magnitude of reduction)
						JKOM	-	-	$p > 0.05$
						NSAIDs necessity	-	-	$p = 0.025$*
Curcuminoid (Curcumin)	Panahi *et al.* (2014)	Iran	Double-blind	**T** n = 19 (5M/14F), age = 57.32±8.78 **P** n = 21 (4M, 17F), age = 57.57±9.05 OA region affected = knee	**T** (1500 mg/d) vs **P**, 6 weeks	WOMAC global score	**T0** = 42.4±18.3 **T1** = 25.0±13 $p < 0.001$*	**P0** = 44.6±17.3 **P1** = 40.6±12.6 $p = 0.072$	$p = 0.001$*
						VAS score	$p < 0.001$*	$p > 0.05$	$p < 0.001$* (magnitude of reduction)
						NSAIDs consumption	-	-	$p < 0.001$* (magnitude of reduction)

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Meriva® (Curcumin)	Belcaro *et al.* (2010)	Italy	Double-blind	**T** n = 50 (23M/27F), age = 43.6±5.5 **P** n = 50 (28M, 22F), age =44.2±6 OA region affected = not specified	**T** (1000 mg/d) vs **P**, 8 months	WOMAC total scores	**T0** = 80.6 **T1** = 33.3 $p < 0.05$*	**P0** = 77.8 **P1** = 68.8 $p > 0.05$	$p < 0.05$*
						Pain medications usage	-	-	$p < 0.05$*
Aflapin (3-acetyl-11-keto-b-boswellic acid)	Vishal *et al.* (2011)	India	Double-blind,	**T** n = 30 (11M/19F), age = 53.2±6.5 **P** n = 29 (11M, 18F), age =55.3±8.8 OA region affected = knee	**T** (100 mg/d) vs **P**, 30 days	VAS score	**T0** = 48.0±6.0 **T1** = 24.5±11.9 $p < 0.000$*	**P0** = 47.6±9.7 **P1** = 39.3±9.5 $p < 0.000$*	$p < 0.000$*
						WOMAC pain score	**T0** = 47.8±12.4 **T1** = 24.2±12.0 $p < 0.000$*	**P0** = 45.9±10.5 **P1** = 40.3±11.4 $p = 0.001$*	$p < 0.000$*
						WOMAC stiffness score	**T0** = 38.8±13.3 **T1** = 20.0±15.6 $p < 0.000$*	**P0** = 37.5±14.9 **P1** = 34.1±15.6 $p = 0.202$	$p = 0.001$*
						WOMAC function score	**T0** = 41.1±11.8 **T1** = 22.5±11.1 $p < 0.000$*	**P0** = 40.6±9.5 **P1** = 36.8±11.5 $p = 0.003$*	$p < 0.000$*
5-Loxin (I) and Aflapin (II) (3-acetyl-11-keto-b-boswellic acid)	Sengupta *et al.* (2010)	India	Double-blind	**TI** n = 19 (3M/16F), age = 51.6±9.9 **TII** n = 19 (7M/12F), age = 53.2±7.9 **P** n = 19 (9M, 10F), age =52.4±7.5 OA region affected = knee	**TI** (100 mg/d) or **TII** (100 mg/d) vs **P**, 90 days	VAS score	**TI0** = 48.2±6.1 **TI1** = 26.2±16.5 $p < 0.000$* **TII0** = 47.7±7.3 **TII1** = 20.2±12.3 $p < 0.000$*	**P0** = 47.7±6.5 **P1** = 38.3±9.0 $p = 0.001$*	$p = 0.006$* (P1 compared to TI1) $p < 0.000$* (P1 compared to TII1)
						WOMAC pain score	**TI0** = 46.1±7.6 **TI1** = 25.3±17.2 p <0.0001* **TII0** = 45.0±13.3 **TII1** = 13.9±8.3 p <0.0001*	**P0** = 44.7±11.5 **P1** = 36.3±10.5 $p = 0.0021$*	$p = 0.009$* (P1 compared to TI1) p <0.0001* (P1 compared to TII1)
						WOMAC stiffness score	**TI0** = 39.5±11.2 **TI1** = 17.1±16.8 $p = 0.000$* **TII0** = 39.5±13.3, **TII1** = 11.8±12.8 $p < 0.000$*	**P0** = 39.5±11.2 **P1** = 29.6±9.5 $p = 0.006$*	$p = 0.006$* (P1 compared to TI1) $p = 0.000$* (P1 compared to TII1)
						WOMAC function score	**TI0** = 43.1±7.8 **TI1** = 25.2±15 $p < 0.000$* **TII0** = 42.0±8.4 **TII1** = 16.2±8.1 $p < 0.000$*	**P0** = 42.0±10.3 **P1** = 32.0±10.8 $p = 0.003$*	$p = 0.078$* (P1 compared to TI1) $p = 0.000$* (P1 compared to TII1)

Table 2. Summary of RCTs of antioxidant and anti-inflammatory dietary supplements for the treatment of OA (Cont.)

Supplements (Bioactive compounds)	Author, year	Country	Study design	Participants characteristics (n, gender, age, OA region affected)	Dosage regime, duration	Outcomes reported	*M*±*SD*, p-value: Treatment group (T0-T1)	Placebo group (P0-P1)	Treatment-Placebo (TI-P1)
5-:Loxin (3-acetyl-11-keto-b-boswellic acid)	Sengupta *et al.* (2008)	India	Double-blind	**TI** n = 24 (7M/17F), age = 52.37±8.37 **TII** n = 23 (8M/15F), age = 53.22±8.73 **P** n = 23 (5M, 18F), age =52.43±9.65 OA region affected = knee	**TI** (100 mg/d) or **TII** (250 mg/d) vs **P**, 90 days	VAS score	**TI0** = 57.1±8.7 **TI1** = 21.4±7.13 *p* < 0.000* **TII0** = 55.6±9.26 **TII1** = 14.2±6.8 *p* < 0.000*	**P0** = 56.9±12.0 **P1** = 41.8±16.0 *p* < 0.05*	*p* < 0.001* (P1 compared to TI1) *p* < 0.001* (P1 compared to TII1)
						WOMAC pain score	**TI0** = 42.1±2.93 **TI1** = 19.2±3.55 *p* < 0.000* **TII0** = 37.2±2.88, **TII1** = 15.2±2.50 *p* < 0.000*	**P0** = 38.0±2.03 **P1** = 31.7±2.58 *p* = 0.121	*p* = 0.009* (P1 compared to TI1) *p* < 0.001* (P1 compared to TII1)
						WOMAC stiffness score	**TI0** = 31.8±3.61 **TI1** = 14.1±3.71 *p* < 0.000* **TII0** = 27.7±3.44 **TII1** = 9.24±2.07 *p* < 0.000*	**P0** = 33.2±2.73 **P1** = 24.5±2.37 *p* = 0.298	*p* = 0.12 (P1 compared to TI1) *p* = 0.014* (P1 compared to TII1)
						WOMAC function score	**TI0** = 41.5±2.31 **TI1** = 24.3±4.28 *p* < 0.000* **TII0** = 38.6±2.32 **TII1** = 17.3±1.98 *p* < 0.000*	**P0** = 41.3±2.02 **P1** = 34.1±1.09 *p* = 0.105	*p* = 0.10 (P1 compared to TI1) *p* = 0.002* (P1 compared to TII1)
Pycnogenol (Proanthocyanidins consisting mainly of procyanidins and phenolic acids)	Farid *et al.* (2007)	Iran	Double-blind	**T** n = 19 (1M/18F), age = 47.5 ± 7.4 **P** n = 18 (1M, 17F), age = 48.9 ± 9.6 OA region affected = knee	**T** (50 mg, TDS) vs **P**, 3 months	WOMAC total scores	**T0** = 1400±482 **T1** = 725±346 *p* < 0.001*	**P0** = 1463±552 **P1** = 1455±509 *p* > 0.05	*p* < 0.001*
						Frequency of medications taken	Reduced. *p* < 0.001*	Increased *p* < 0.001*	-
						Dosage of medications taken	Reduced *p* < 0.001*	Increased *p* < 0.05*	-
	Belcaro *et al.* (2008a)	Italy	Double-blind	**T** n = 77 (39M/38F), age = 48.6 ± 8 **P** n = 79 (39M, 40F), age = 47.8 ± 7.7 OA region affected = not specified	**T** (50 mg, BD) vs **P**, 3 months	WOMAC total scores	**T0** = 79.2 **T1** = 34.6 *p* < 0.05*	**P0** = 76.9 **P1** = 69.5 *p* > 0.05	*p* < 0.05*
						Medication use			*p* < 0.05*

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Supplements (Bioactive compounds)	Author, year	Country	Study design	Participants characteristics (n, gender, age, OA region affected)	Dosage regime, duration	Outcomes reported	*M*±*SD*, p-value: Treatment group (T0-T1)	Placebo group (P0-P1)	Treatment-Placebo (TI-P1)
Pycnogenol (Proanthocyanidins consisting mainly of procyanidins and phenolic acids)	Cisár *et al.* (2008)	Slovakia	Double-blind	**T** n = 50 (14M/36F), age = 54 (25-65) **P** n = 50 (18M, 32F), age = 54 (30-65) OA region affected = knee	**T** (50 mg, TDS) vs **P**, 3 months	WOMAC total scores	$p < 0.05$*	$p < 0.05$*	$p < 0.05$*
						VAS	$p < 0.05$*	$p > 0.05$	$p < 0.05$*
Rose hip (galactolipid)	Ginnerup-Nielsen *et al.* (2015)	Denmark	Double-blind	**T** n = 50 (18M/32F), age = 67.5±9.0 **P** n = 50 (15M/35F), age = 66.12±9.69 OA region affected = knee or hip	**T** (750 mg/d) vs **P**, 12 weeks	KOOS Function, QoL, Pain, Symptoms, Sports/ Recreation	-	-	$p > 0.05$
						SF-36 mental health, physical health	-	-	$p > 0.05$
Rose hip (galactolipid)	Warholm *et al.* (2003)	Norway	Double-blind	**T** n = 48 (15M/33F), age = 65.5±14.2 **P** n = 48 (19M/29F), age = 65.8±14.7 OA region affected = knee or hip	**T** (5 g/d) vs **P**, 4 months	Joint pain	-	-	$p = 0.035$*
						NSAIDs use	$p < 0.016$*	$p > 0.05$	$p > 0.05$
PFP extract (Cyanidin-3-O-glucoside, quercetin -3-O-glucoside, and edulilic acid)	Farid *et al.* (2010)	New Zealand	Double-blind	**T** n = 17 (5M/12F), age = 55±14.1 **P** n = 16 (3M/13F), age = 49.71±14.0 OA region affected = knee	**T** (150 mg/d) vs **P**, 2 months	WOMAC total scores	**T0** = 120±23.4 **T1** = 97.1±22.6	**P0** = 121±33.9 **P1** = 150±42.4	$p < 0.001$*
L-carnitine	Malek Mahdavi *et al.* (2016)	Iran	Double-blind	**T** n = 33 (33F), age = 51.63±5.69 **P** n = 36 (36F), age = 52.44±6.56 OA region affected = knee	**T** (750 mg/d) vs **P**, 8 weeks	VAS pain score	$p < 0.001$*	$p < 0.001$*	$p = 0.002$*
	Malek Mahdavi *et al.* (2015)	Iran	Double-blind	**T** n = 33 (33F), age = 51.63±5.69 **P** n = 36 (36F), age = 52.44±6.56 OA region affected = knee	**T** (750 mg/d) vs **P**, 8 weeks	VAS pain score	$p < 0.001$*	$p = 0.012$*	$p < 0.001$*

Table 2. Summary of RCTs of antioxidant and anti-inflammatory dietary supplements for the treatment of OA (Cont.)

Supplements (Bioactive compounds)	Author, year	Country	Study design	Participants characteristics (n, gender, age, OA region affected)	Dosage regime, duration	Outcomes reported	*M*±*SD*, p-value: Treatment group (T0-T1)	Placebo group (P0-P1)	Treatment-Placebo (TI-P1)
ART extract (Artemisinin)	Hunt *et al.* (2016)	New Zealand	Double-blind	**HD** n = 14 (9M/5F), age = 66.2±9.50 **LD** n = 14 (7M/7F), age = 62.9±7.55 **P** n = 14 (6M/8F), age = 59.6±9.98 OA region affected = knee or hip	**HD** (600 mg/d), **LD** (300 mg/d) vs **P**, 12 weeks	WOMAC total scores	**HD0 vs HD1** $p = 0.365$ **LD0 vs LD1** $p = 0.016$*	$p = 0.103$	
						VAS pain scores	**HD0 vs HD1** $p = 0.176$ **LD0 vs LD1** $p = 0.008$*	$p = 0.367$	
DBE (Hydroxyproline, collagen, chondroitin sulfate, and ganglioside)	Shin *et al.* (2018)	Korea	Double-blind	**T** n = 24 (9M/15F), age = 59.9±1.4 **P** n = 26 (8/18F), age = 57.7±1.2 OA region affected = knee	**T** (550 mg/d) vs **P**, 12 weeks	WOMAC total scores	$p < 0.001$*	$p = 0.025$*	$p = 0.135$
						VAS pain scores	$p = 0.017$*	$p = 0.078$	$p = 0.325$
Garlic (allicin)	Salimzadeh *et al.* (2018)	Iran	Double-blind	**T** n = 39 (39F), age = 58.9±7.5 **P** n = 26 (26F), age = 58.5±7.4 OA region affected = knee	**T** (1000 mg/d) vs **P**, 12 weeks	WOMAC total scores	**T0** = 38.4±15.9 **T1** = 30.6±15.7 $p = 0.004$*	**P0** = 39.5±14.1 **P1** = 35±14.6 $p = 0.094$	$p = 0.295$
	Dehghani *et al.* (2018)	Iran	Double-blind	**T** n = 39 (39F), age = 58.9±7.5 **P** n = 26 (26F), age = 58.5±7.4 OA region affected = knee	**T** (1000 mg/d) vs **P**, 12 weeks	VAS pain scores	**T0** = 6.8±2 **T1** = 5.3±2.3 $p = 0.002$*	**P0** = 6.7±2.4 **P1** = 6.2±2.5 $p = 0.674$	$p = 0.043$*
Momordica charantia (bitter melon) (Alkaloids, saponin, glycosides, steroids, sterol and phenolic compounds (flavonoids), tannin)	Lim *et al.* *(2018)*	Malaysia	Single-blind	**T** n = 38 (15M/23F), age = 61.97±9.19 **P** n = 37 (9M/28F), age = 57.81±9.15 OA region affected = knee	**T** (4500 mg/d) vs **P**, 3 monhs	KOOS score			
						Pain	**T0** = 62.2±15.4 **T1** = 82.2±11.2 $p < 0.001$*	**P0** = 68.4±21.0 **P1** = 76.2±18.0 $p = 0.026$*	$p > 0.05$ $p > 0.05$
						Symptoms	**T0** = 56.6±20.9, **T1** = 77.2±17.3 $p < 0.001$*	**P0** = 66.3±13.6 **P1** = 71.7±19.2 $p = 0.120$	$p > 0.05$ $p > 0.05$
						ADL	**T0** = 62.2±19.0 **T1** = 79.9±16.0 $p < 0.001$*	**P0** = 68.1±18.7 **P1** = 75.1±18.7 $p = 0.118$	$p > 0.05$ $p > 0.05$
						Sport/Rec	**T0** = 36.7±27.0 **T1** = 56.1±27.0 $p < 0.001$*	**P0** = 30.7±21.0 **P1** = 47.5±20.0 $p < 0.001$*	$p > 0.05$ $p > 0.05$
						QoL	**T0** = 46.5±18.9 **T1** = 70.6±20.6 $p < 0.001$*	**P0** = 53.0±22.7 **P1** = 59.7±20.1 $p = 0.019$*	$p > 0.05$ $p > 0.05$

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Table 2. Summary of RCTs of antioxidant and anti-inflammatory dietary supplements for the treatment of OA (Cont.)

Supplements (Bioactive compounds)	Author, year	Country	Study design	Participants characteristics (n, gender, age, OA region affected)	Dosage regime, duration	Outcomes reported	*M*±*SD*, p-value: Treatment group (T0-T1)	Placebo group (P0-P1)	Treatment-Placebo (TI-P1)
Argan oil (80% MUFA and 20% SFA. Minor components: polyphenols, tocopherols, sterols, squalene, and triterpene alcohols)	Essouiri *et al.* (2017)	Morocco	Double-blind	**T** n = 55 (4M/51F), age = 58.24±8.8 **P** n = 52 (3M/49F), age = 58.85±5.6 OA region affected = knee	**T** (30 ml/d) vs **P**, 8 weeks	WOMAC total scores	**T0** = 26.3±12.7 **T1** = 20.2±12.6 $p < 0.001$*	**P0** = 23±9.75 **P1** = 26.5±9.4 $p < 0.001$*	$p < 0.000$*
						VAS pain score	**T0** = 47.3±15.2 **T1** = 32.4±13.9 $p < 0.001$*	**P0** = 48±115 **P1** = 50.2±16.9 $p = 0.2$	$p = 0.02$*
						LFI	**T0** = 5.50±2.83 **T1** = 4.49±2.18 $p < 0.001$*	**P0** = 5.84±2.6 **P1** = 6.1±2.8 $p = 0.96$	$p < 0.000$*
Liquorice flavonoid oil (Glabridin: hydrophobic polyphenols)	Kinoshita *et al.* (2017)	Japan	Double-blind	**T** n = 26 (5M/21F), age = 74.6±9.8 **P** n = 24 (2M/22F), age = 73.3±9.7 OA region affected = knee	**T** (300 mg/d) vs **P**, 16 weeks	VAS pain score	**T0** = 34.0±22.6, **T1** = 27.8±25.9 $p = 0.08$	**P0** = 47.5±22.8 **P1** = 32.7±23.7 $p < 0.01$*	$p = 0.025$*
						JKOM scores	**T0** = 33.0±19.2, **T1** = 26.2±19.9 $p < 0.01$*	**P0** = 34.7±14.1 **P1** = 28.5±17.9 $p = 0.03$*	p = 0.99
Ginger (gingerols and shogaols)	Alipour *et al.* (2016)	Iran	Double-blind	**T** n = 37 (29M/8F), age = 58.6±50 **P** n = 35 (28M/7F), age = 57.7±68 OA region affected = knee	**T** (1000 mg/d) vs **P**, 12 weeks	VAS pain score	**T0** = 7.78±2.90 **T1** = 2.18±2.59 $p = 0.001$*	**P0** = 7.50±2.72 **P1** = 4.9±3.04 $p = 0.001$*	$p = 0.001$*
	Niempoog *et al.,* (2012)	Thailand	Double-blind	**T** n = 26 (5M/21F), age = 48.88±7.35 **P** n = 23 (2M/21F), age = 49.09±8.03 OA region affected = knee	**T** (1000 mg/d) vs **P**, 8 weeks	KOOS scores:			
						Pain			$p > 0.05$
						Symptoms			$p > 0.05$
						Daily activity			$p > 0.05$
						Sport/Rec			$p > 0.05$
						QoL			$p > 0.05$
	Zakeri *et al.* (2011)	Iran	Double-blind	**T** n = 103 (20M/83F), age = 48.4±11.1 **P** n = 101 (20M/81F), age = 45.74±12.5 OA region affected = knee	**T** (500 mg/d) vs **P**, 6 weeks	VAS pain score			
						Standing	**T0** = 57.3±15.2 **T1** = 38.7±18.5	**P0** = 58.1±14.7 **P1** = 44.8±18.6	$p = 0.008$*
						After walking 50 m	**T0** = 59.8±16 **T1** = 39.4±16.6	**P0** = 61.2±16.5 **P1** = 46.5±18.8	$p = 0.012$*
						WOMAC scores			
						Stiffness	**T0** = 2.1±0.7 **T1** = 1.4±0.6	**P0** = 2.0±0.6 **P1** = 1.8±0.6	$p = 0.003$*
						Difficulty	**T0** = 2.6±2.0 **T1** = 0.4±0.6	**P0** = 2.6±0.5 **P1** = 2.2±0.6	$p = 0.003$*

Table 2. Summary of RCTs of antioxidant and anti-inflammatory dietary supplements for the treatment of OA (Cont.)

Supplements (Bioactive compounds)	Author, year	Country	Study design	Participants characteristics (n, gender, age, OA region affected)	Dosage regime, duration	Outcomes reported	*M*±*SD*, p-value: Treatment group (T0-T1)	Placebo group (P0-P1)	Treatment-Placebo (TI-P1)
Ginger (gingerols and shogaols)	Altman and Marcussen (2001)	US	Double-blind, multicenter	**T** n = 124 (50M/74F), age = 64.0±11.5 **P** n = 123 (45M/78F), age = 66.3±11.6 OA region affected = knee	**T** (510 mg/d) vs **P**, 6 weeks	VAS pain score			
						Standing	-	-	$p = 0.005$*
						After walking 50 feet	**T0** = 49.9±24.3 **T1** = 34.6±29.5	**P0** = 53.1±25.1 **P1** = 44.2±28.3	$p = 0.016$*
						WOMAC total scores	**T0** = 50.2±19.0 **T1** = 37.3±25.1	**P0** = 52.3±18.4 **P1** = 43.5.±23.3	$p = 0.087$
Pomegranate juice (polyphenols, tannins (ellagic acid derivatives) and anthocyanin (prodelphinidins)	Ghoochani *et al.* (2016)	Iran	Double-blind	**T** n = 19 (2M/17F), age = 56.74±10.23 **P** n = 19 (2M/17F), age = 53.84±11.95 OA region affected = knee	**T** (200 ml/d) vs **P**, 6 weeks	WOMAC total scores	**T0** = 39.6±15.9 **T1** = 32.4±16.6 $p = 0.01$*	**P0** = 39.0±20.7 **P1** = 40.6±20.5 $p = 0.22$	$p = 0.18$
Sesame seed (lignans: sesamin and sesamolin)	Eftekhar Sadat *et al.* (2013)	Iran	Double-blind	**T** n = 22, age = 56.90±6.39 **P** n = 23, age = 58.27±7.84 OA region affected = knee	**T** (40 g/d) vs **P**, 2 months	VAS pain intensity	-	-	$p = 0.004$*
						Mean KOOS score	$p = 0.001$*	$p = 0.001$*	$p = 0.009$*
Phytalgic® (fish oils, urtica dioica, zinc, and vitamin E)	Jacquet *et al.* (2009)	France	Double-blind	**T** n = 41 (14M/27F), age = 56.8 (28-79) **P** n = 40 (12M/28F), age = 57.5 (28-84) OA region affected = knee or hip	**T** (3 capsules/d) vs **P**, 3 months	Mean use of analgesics	**T0** = 19.8 **T1** = 6.5 $p < 0.05$*	**P0** = 19.1 **P1** = 16.5 $p > 0.05$	$p < 0.001$*
						Mean use of NSAIDs	**T0** = 1.30 **T1** = 0.36	**P0** = 1.13 **P1** = 1.03	$p = 0.02$*
						WOMAC total scores	**T0** = 1001 **T1** = 430	**P0** = 1015 **P1** = 1085	$p < 0.001$*
Aquamin (calcium and magnesium-rich seaweed-derived multi-mineral supplement (polyphenols)	Frestedt *et al.* (2009)	USA	Double-blind	**T** n = 8 (1M/7F), age = 62.5±5.3 **P** n = 14 (6M/8F), age = 62.9±11.4 OA region affected = knee	**T** (2400 mg/d) vs **P**, 12 weeks	WOMAC scores:			
						Pain	-	-	$p = 0.63$
						Stiffness	-	-	$p = 0.83$
						Physical function	-	-	$p = 0.43$
						Composite	-	-	$p = 0.47$

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Supplements (Bioactive compounds)	Author, year	Country	Study design	Participants characteristics (n, gender, age, OA region affected)	Dosage regime, duration	Outcomes reported	*M*±*SD*, p-value		
							Treatment group (T0-T1)	Placebo group (P0-P1)	Treatment-Placebo (TI-P1)
Soy protein (genistein and daidzein: the prominent soy isoflavones)	Arjmandi *et al.* (2004)	USA	Double-blind	**T** n = 44 (24M/20F), age = 60.5±1.8 **P** n = 44 (22M/22F), age = 60.7±1.8 OA region affected = knee	**T** (40 g/d) vs **P**, 3 months	Use of pain medication	$p < 0.05$*	$p > 0.05$	-
						Pain level	$p < 0.05$*	$p > 0.05$	-
Willow bark extract (salicin)	Schmid *et al.* (2001)	Germany	Double-blind	**T** n = 39 (30M/9F), age = 52.4±7.0 **P** n = 39 (29M/10F), age = 53.5±10.5 OA region affected = knee or hip	**T** (240 mg/d) vs **P**, 2 weeks	WOMAC pain scores	**T0** = 34.1±19.3 **T1** = 29.3 $p = 0.49$	**P0** = 44.1±26.5 **P1** = 45.1 $p = 0.13$	$p = 0.047$*
CFB (Boric acid ester of fructose)	Pietrzkowski *et al.* (2014)	USA	Double-blind	**T** n = 30 (15M/15F), age = 48.5±1.6 **P** n = 30 (15M/15F), age = 51.4±1.2 OA region affected = knee	**T** (220 mg/d) vs **P**, 2 weeks	WOMAC score	**T0** = 53.57±13.69 **T1** = 38.17±10.11 $p < 0.003$*	**P0** = 52.70±12.66 **P1** = 51.03±10.36 $p > 0.05$	$p < 0.000$*

affects the whole joint by destroying the articular cartilage, altering the underlying subchondral bone structure, and inducing the chronic inflammation of synovium (Ashford and Williard, 2014). The destruction of articular cartilage results in reduced capability to distribute a large burden and minimize friction between the joint spaces. Subsequently, a bone will come in contact with an opposing bony surface directly due to reduced joint space. Over time, new osteophytes will be formed, which generate a chronic inflammatory process in which cytokines and matrix metalloproteinases (MMP) are released into the joint (Birrell and Oliver, 2010).

The cytokines responsible include the inflammatory interleukins (IL) (e.g. IL-1β, IL-6, IL-15, IL-17 and IL-18), tumor necrosis factor-alpha (TNF-α), and anti-inflammatory interleukins (e.g. IL-4, IL-10 and IL-13) (Grover and Samson, 2016). The raise in IL-1 damages the articular cartilage, while TNF-α poses a similar effect and in synergy with IL-1β actions (Wojdasiewicz *et al.,* 2014). The net outcome is the inhibition of the proteoglycan component production, which are the proteins that will bind the proteoglycans and type-II collagen in chondrocytes (Séguin and Bernier, 2003). The activated chondrocytes synthesize the matrix MMPs, such as MMP-1, MMP-3 and MMP-13 (Wojdasiewicz *et al.*, 2014). Moreover, IL-6 exerts similar effects on the cartilage and in synergy with that of other inflammatory cytokines, resulting in reduced production of type-11 collagen and increased MMP activity (Porée *et al.,* 2008). Both IL-1β and TNF-α also induce the synthesis of inflammatory mediators prostaglandin E2 (PGE2) and cyclooxygenase-2 (COX-2) (Kapoor *et al*., 2011).

Meanwhile, another cause which is the oxidative stress interrupts the cartilage homeostasis and leads to increased cartilage breakdown (Salimzadeh *et al.*, 2018). Concurrently, reactive oxygen species (ROS) induce the synthesis of matrix-degrading enzymes and disrupt the matrix production (Im *et al., 2*007, 2008). Besides, IL-1β induces the synthesis of ROS-like peroxides and hydroxylated radicals, generation of nitric oxide (NO), and causes the insufficiency of superoxide dismutase (SOD) and catalase. The inadequacy of SOD causes an increased concentration of superoxide in which a reaction between NO and superoxide will produce peroxynitrite that consequently destroys the telomere by targeting guanine repeats in the DNA telomeres. This results in reduced collagen II production (Regan *et al.,* 2008). Moreover, catalase reduction causes peroxide to accumulate, leading to increased lipid peroxidation due to the synthesis of 4-hydroxynonenal. 4-hydroxynonenal consequently increases the concentration of factors that stimulate collagen II breakdown and suppress its expression. Therefore, cartilage destruction will ensue in OA patients (Morquette *et al*., 2006).

Currently, there is no cure for OA, thus rendering its management to focus on symptom relief (Anandacoomarasamy and March, 2010), improvement of quality of life, and prevention of progression (Selten *et al*., 2017). Pain is the principal symptom among OA patients, with various evidence reporting the pain they experience to be related to inflammation and oxidative stress, cartilage destruction, and joint space narrowing (Andriacchi and Favre, 2014; Muraki *et al.,* 2015). Thus, antioxidant and anti-inflammatory dietary supplements play a vital role to improve such symptoms. The mechanism of action of these dietary supplements can be explained based on the bioactive compounds present within them.

In this scoping review, the bioactive compounds found in the supplements which demonstrated positive impacts are predominantly polyphenols. Polyphenols are found abundantly in plants and vegetables, possessing strong anti-inflammatory and free radical scavenging antioxidant activity (González *et al*., 2011). Their antioxidant activity is influenced by the structure of the functional groups (Hussain *et al*., 2016), whereby the mechanism behind activities, such as radical scavenging and metal ion chelation, is dependent on the number of hydroxyl groups present (Kelly *et al.,* 2002). Meanwhile, antioxidants can prevent OA progression by scavenging the ROS (Grover and Samson, 2016), retarding the enzymes involved in ROS production and upregulation or protection of antioxidant defenses (Mishra *et al*., 2013).

Whereas, the anti-inflammatory properties of phenolic compounds, such as flavonoids could are exhibited by suppressing PGE2 synthesis, COX-2 expression, and inducible microsomal prostaglandin E synthase-1 (mPGES-1) expression (Hämäläinen *et al.*, 2011). This can lead to significant pain reduction among OA patients (Bensen *et al*., 1999). Besides, pain relief is attributed to the anti-nociceptive activity of flavonoid and tannin (Ghogare *et al.*, 2009). In vitro and in vivo studies have reported that phenolic compounds can delay OA development and progression by altering the related metabolic and biochemical processes, including suppressing the synthesis of pro-inflammatory cytokines, such as IL-1β, IL-6, TNF-α and PGE2 in the affected joints (Murakami *et al.*, 2007; Ahmed, 2010). In addition, flavonoids examined in vivo inhibit inducible NO synthase, suppress NO production and neutralize other reactive nitrogen species (RNS) and ROS-like superoxide (Adhikari *et al.*, 2011) involved in inducing inflammatory gene expression (Tseng-Crank *et al*.,

2010).

Next, the long chain omega-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are also the bioactive ingredient responsible for its beneficial effects. Both of these fatty acids exert anti-inflammatory effect by inhibiting the inflammatory genes expression via the suppression of pro-inflammatory transcription factor nuclear factor kappa B (Calder, 2015). Besides, L-carnitine showed the anti-inflammatory activity by lowering the inflammatory factors such as IL-1β which subsequently lead to pain reduction and physical function improvement (Malek Mahdavi et al., 2016). In addition, 3-O-acetyl-11-keto-beta-boswellic acid (AKBA), the active ingredient of BSE is a powerful inhibitor of 5-lipoxygenase (5-LOX) activity (Suva *et al.,* 2017) which can reduce pain and inflammation associated with OA (Suva *et al.*, 2018).

Moreover, ASU is the remaining oily extracts derived from the soap production which contain phytosterols, triterpenoids and lipophilic vitamins (Goudarzi *et al.*, 2018). ASU can minimize PGE2 and NO production which related to pain and inflammation (Goudarzi *et al.*, 2017). CFB is a patented complex of boron, fructose and calcium found ubiquitous in plants (Reyes-Izquierdo *et al.,* 2012). CFB can reduce serum levels of C-reactive protein (CRP) which associated with inflammation-related conditions such as OA (Scorei and Scorei, 2013). Ganglioside derived from DBE can inhibit the expression of MMPs in IL-1β-induced OA which stimulate the accumulation of type II collagen (Suh *et al*., 2016).

While this scoping review provides the best evidence regarding the effectiveness of specific pharmacological treatments when assessing single supplements or supplements with similar chemical components, it should be interpreted with caution due to several limitations (Freedman, 1990). For most of the supplements examined, the number of studies conducted for each supplement is relatively small with a maximum of four studies in clinical trials involving ginger and curcumin supplementation, respectively. Secondly, most of the studies provided information on knee OA, thus reducing the concluding generalizability for other types of OA. Furthermore, more than half of the studies were followed up in short term duration (≤ three months), thereby rendering the efficacy of these supplements in medium and long term durations as uncertain. Hence, it is necessary to carry out RCTs having a longer intervention duration to further confirm the efficacy of these supplements. Moreover, it is noticed that there was unequal gender distribution in most of the studies in which there were more female participants compared to male participants. This might be due to the fact that women had a higher risk of getting OA compared to men which result in higher OA incidence among women. This was attributable by the estrogen deficiency particularly after menopause (Venkatachalam et al., 2018). Last but not least, the biochemical parameters and safety issues of these supplements were not investigated.

5. Conclusion

Overall, out of the 24 dietary supplements identified, most of them demonstrated beneficial effects on the clinical signs and symptoms. These dietary supplements were krill oil, ASU, curcumin, BSE, Pycnogenol, PFP extract, L-carnitine, ART, DBE, garlic, Momordica charantia, argan oil, ginger, PJ, sesame seed, Phytalgic®, soy protein and CFB. In contrast, Aquamin supplementation did not exert positive impacts on OA management, while inconsistent findings were observed in the case of GLM extract, vitamin E, MSM, LFO, ginger, willow bark extract and rose hip supplementation. Since this scoping review noticed that there was very limited study which explored the efficacy of antioxidant and anti-inflammatory dietary supplements to manage OA in Association of Southeast Asian Nations (ASEAN) countries. Hence, future researchers need to collaborate and address this identified gap by examining the effectiveness of these supplements towards OA patients among ASEAN populations.

Conflict of Interest

The authors declare no conflict of interest.

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