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Review Article

Effectiveness of Complementary and Alternative Medicine and Physical Therapies in Peripheral Arterial Disease with Intermittent Claudication: A Systematic Review

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ABSTRACT

Aim/Background: Peripheral Arterial Disease (PAD) affects the lower limbs. Globally there is a growing disease burden among the patients suffering from cardio-vascular disease and metabolic disorders. The purpose of this review is to generate evidence on the efficacy of CAM therapies in PAD. **Materials and Methods:** This systematic review was performed across the five electronic databases i.e. PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid SP, ISI Web of Science, Elsevier Science Direct, and Wiley Online Library as per the PRISMA guidelines from inception till April 2022. **Results:** After screening *n*=55,410 articles, *n*=77 articles were found to fulfill the eligibility criteria and were selected for this review. The nature of interventions investigated in the clinical trials were physical interventions including exercises of different forms, oral supplements, and other interventions such as chelation therapy, Tai Chi Chuan (TCC), Intermittent Mechanical Compression (IMC) device, connective tissue reflex massage, Remote Ischemic Preconditioning (RIC), Transcutaneous Electrical Nerve Stimulation (TENS) and heat therapy. Upon final assessment, it was revealed that physical activity had a positive effect on peripheral arterial disease patients' quality of life. In addition,*Ginkgo biloba* and nitrate supplements were found effective for Intermittent Claudication (IC) and PAD patients. **Conclusion:** This review suggests a positive impact of physical activity on peripheral arterial disease patients' quality of life. Evidence also shows that Physical activity/ exercise-based intervention alone or in combination with the supplement is found to be effective among PAD patients and has shown significant results in intermittent claudication.

Keywords: Peripheral arterial disease, Complementary medicine, Alternative medicine, Review, Intermittent claudication.

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INTRODUCTION

Peripheral Arterial Disease (PAD) is atherosclerotic of arteries) (i.e. the abdominal aorta, iliac, and arteries of the lower limbs) which leads to the narrowing and blocking of arteries.[1,2] PAD is more prevalent in the lower extremities and narrowing or blockage of the vessels resulting in pain, aches, or cramps with walking (claudication) can happen in the buttock, hip, thigh, or calf.[3] Globally more than 200 million people are affected PAD.[4,5]{Fowkes, 2013 #468} Negligence in timely diagnosis is one of the main factors which result in complications such as Claudication,[6] rest pain, and ulcers due to ischemia,[7] recurrent hospitalization, revascularization,[8] and even loss of limbs.[9] In addition, PAD doubles the risk of myocardial infarction, stroke, and cardiovascular death, and the all-cause mortality is

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increased as compared to patients without PAD.[10-12] According to the World Health Organization (WHO), it is estimated that 58% of all the deaths in low-middle-income countries are due to non-communicable diseases, and among them, the highest rate of death i.e. 29% is due to cardiovascular diseases.[13] The management and treatment option available for PAD range from effective management of modifiable risk factor,[14] pharmacological therapy,[15] and surgical or endovascular interventions.[2] However, it is observed that most of the PAD patients use Complementary and Alternative Medicine (CAM) instead of conventional treatment. As per the definition of CAM by Cochrane Collaboration "Complementary and alternative medicine (CAM) is a *broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in each historical period.*[16] CAM includes all such practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being"[17] Some of the common practices that are practiced worldwide are aromatherapy, exercise, massage therapy, phytotherapy, yoga, acupuncture, herbal medicine and many others.[16,18-21] Reasons for use of CAM includes cultural and historical values, lack of access to conventional therapy, or the expenses associated with the cost of modern treatments.

Therefore a substantial number of the patients suffering from chronic diseases are more inclined towards the use of CAM.[21] From the literature it is evident that a huge variety of CAM is used by patients suffering from PAD. Some of the CAM was also investigated as comparative intervention alone or in conjunction with the medical interventions. However, to date there is a lack of any systematic evidence that sums up all the published articles and concludes about the effectiveness of CAM in PAD. Hence the purpose of this review is to explore various CAM therapies available and to generate evidence that these therapies are effective for managing the disease.

MATERIALS AND METHODS

Systematic reviews are an ideal approach when there is huge information in a body of literature on a given topic and the researcher are aiming to get an opinion/ overview regarding the volume of literature and studies in line with the focus of the question under investigation. It is a useful scientific method for the investigative or emergent evidence when it is still unclear and more precise method i.e. systematic review with a very specific question cannot be implemented.[22]

This review was performed according to PRISMA guidelines. An online systematic literature search was done from the time of database inception till April 2022. Five electronic databases i.e. PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid SP, ISI Web of Science, Elsevier Science Direct, and Wiley Online Library**.** The search terms were "Alternative medicine" or "Complementary medicine" or "Dietary supplements" or "Herbal medicine" or "Phytotherapy" or "Homeopathy" or "Acupuncture" or "Padma 28" or "*Gingko biloba*" or "Chelation therapy" or "Medicinal plants" or "Massage therapy" or "Exercise Therapy" and "Peripheral arterial disease" or "Peripheral arterial occlusive disease" or "Intermittent Claudication" or Chronic limb-threatening ischemia. The protocol for this review is published at INPLASY systematic review registry [Reg No. INPLASY202330001, DOI number is 10.37766/inplasy2023.3.0001].[23]

Inclusion and Exclusion Criteria

PICOT framework was adopted to define the inclusion criteria (Table 1). All randomized control trials evaluating the effect of any CAM therapy for PAD patients published in the English language were included in this review. All Cross-sectional study, Cohort study, longitudinal study, Case reports, case series, systematic reviews, Meta-analysis, letters to editors were excluded from this review.

Study Selection

The titles and abstracts of the studies were screened to determine whether they met the inclusion criteria. In circumstances where further information was required to decide the full text of the article was read. Any conflict regarding the selection of study was resolved with mutual consensus. Authors were also contacted in the case if some further information was required.

Data Extraction

Expert panel was comprised of three member (Mohammed Kanan Alshammari, Khansa Hamza Hussain and Abdullah Ayed Alshammari) who were responsible for resolving conflict among the authors regarding the data extraction and risk of bias and also assisting in deciding the type of data to be extracted and finalization of the data extraction sheet. Remaining members were divided in to three groups (each comprised of four members), each group was assigned the final papers for extraction on the physical intervention, supplements and miscellaneous therapies. A structure data extraction format was used to gather information required for the review. Main information that was extracted was author's name, publication year, study title, place of study, study design, population characteristics (sample size and mean age), duration of study, intervention comparator, and outcome. The outcomes were addressed as changes in parameters from baseline until the end of the intervention for both the control/placebo and intervention groups. In addition, any other relevant information which was noticed to be relevant to the scope of this systematic review was extracted and discussed in the results section.

Risk of Bias (Quality) Assessment

The risk of bias assessment is one of the essential parameters in concluding about the quality of the clinical trials (Cochrane Chapter 8).[24,25] As per the recommendation of Cochrane, risk of bias tool for the clinical trials[26] was used. Data from the individual clinical trials were extracted and initial assessment was completed by the assigned group regarding the six i.e. sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues. The assessment was independently conducted by two groups of researchers and verified by the others and the grading for each domain was done using Cochrane guidelines in to "high risk," "low risk" or "unclear risk". If the bias would seriously alter the results, then it was rated as high risk. If the bias was unlikely to affect the results, then low risk, and if the effects of bias on results were unclear then the unclear risk of bias. Any conflict in determining this risk by the two groups was resolved with mutual consensus by the expert panel.

Data Analysis

Both qualitative and quantitative approach as recommended by the Cochrane was adapted to summaries the result of this systematic review. To ensure the better presentation of the results section, all the studies were broadly classified into three categories i.e.,

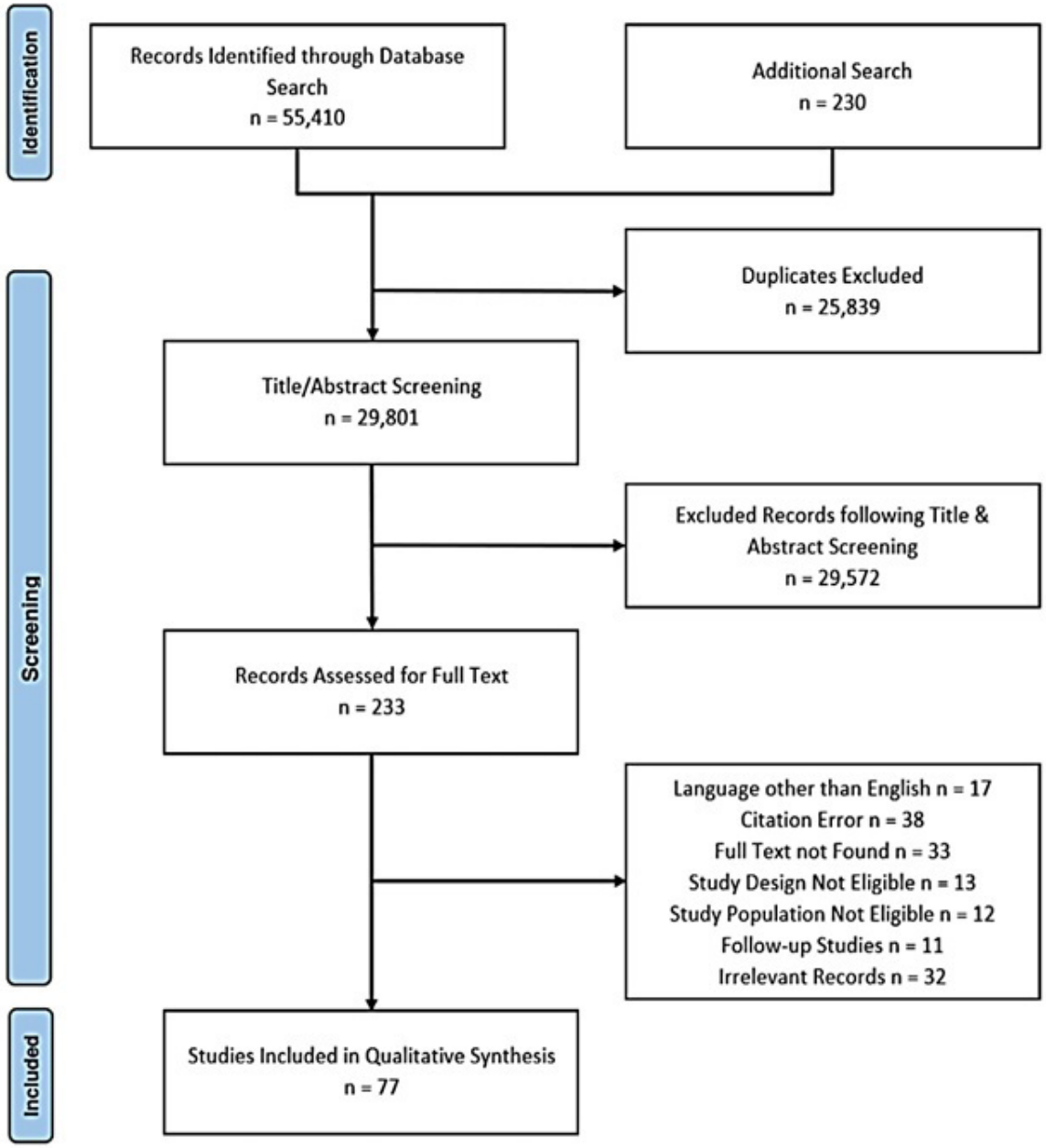

Figure 1: PRISMA flow diagram.

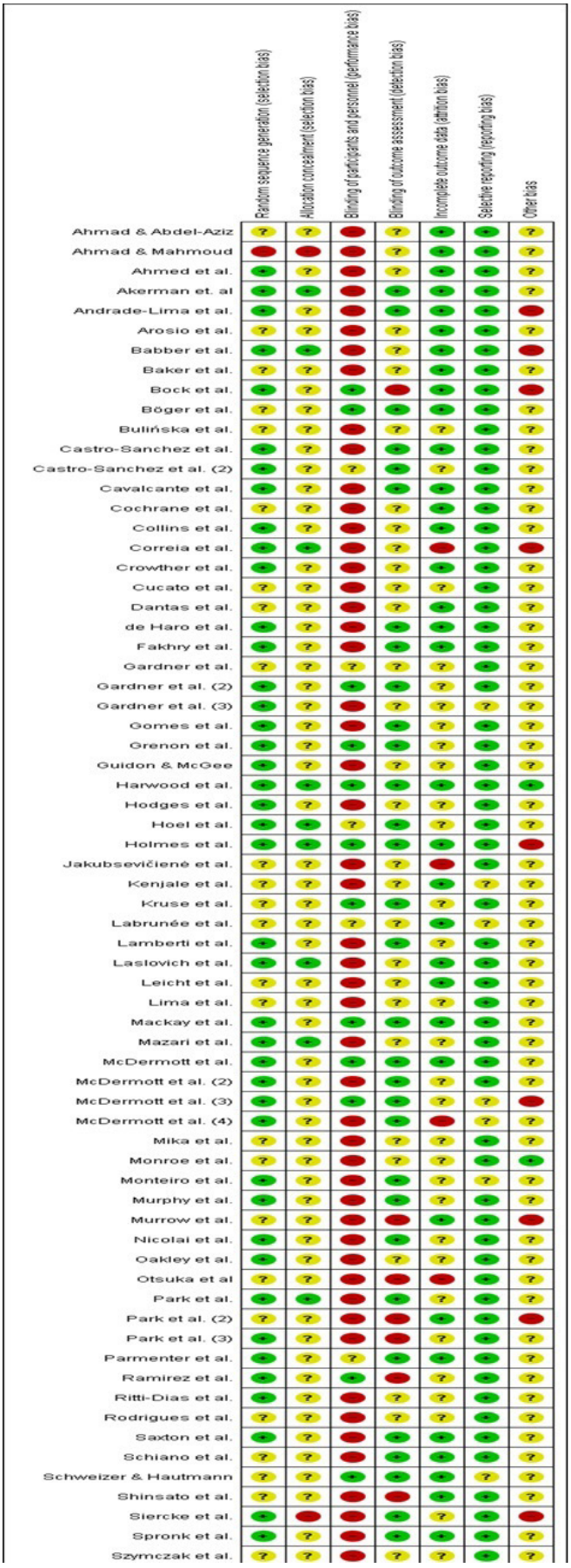

Figure 2: Risk of Bias of Individual Studies.

physical intervention, oral supplements, and other interventions. This classification was based on the interventions used among the selected studies. Further sub-group classifications were also done where necessary to create a pool of studies with similar interventions so that the combined effect could be estimated. The interpretation was performed using evidence-based medicine guidelines by Cochrane. Data analysis for risk of bias was done using Microsoft Excel 365 and Review Manager 5.4.

RESULTS

Upon comprehensive search across the selected databases 55,640 articles were identified. These articles were transferred to ENDNOTE version 19® and duplicates were removed. A total of 25,839 articles were duplicated and were removed. After that in depth screening of articles were performed and 29,801 Titles/Abstracts were screened of whom 233 studies were selected for full text screening. Finally, 77 studies were included in this systematic review as they met the inclusion criteria as shown in the PRISMA flow diagram (Figure 1). Description of Included Studies:

Upon assessment it was revealed that n=66[27-92] were parallel design RCTs while n=11[93-103] were crossover design RCTs. Of all the studies, n= 11[40,41,43,49,52,54,58,68,77,79,87] were single-blinded RCTs while n=17[35,36,48,50,56,63-65,76,80,85,86,88-91,99] were double-blinded RCTs. Assessing the geographic background of the studies revealed that 19 studies were conducted in USA,[34,35,40,46-48,50,56,58,62-65,67,69,70,76,96,101] 10 each in UK[33,45,52,53,61,78,84,92,99,100] and Brazil,[31,42,49,58,68,77,93,95,98,102] 6 in Australia,[41,59,75,88-91] 4 in Italy,[32,57,79,85] 3 each in New Zealand,[30,86,94] Spain,[38,39,43] Poland[37,66,83] and Netherlands,[44,71,82] 2 each in Egypt,[27,28] Ireland,[29,51] Japan,[72,81] South Korea,[73,74] Germany[36,80] and Norway[54,87] and 1 each in Lithuania,[55] France[97] and Denmark.[103]

Characteristics of Participants

A total of 4942 PAD patients participated among the 77 studies included in this systematic review. The sample size of the selected studies ranged from n=7 to n=305.

Risk of Bias Assessment Outcomes

Maximum of the studies (80%) have minimal risk of bias in selective reporting while 60% of the studies have minimal risk of bias in randomization shown in Figure 2. Most studies are free of elevated risk of bias while more than 85% of studies have undetermined allocation. concealment and other risks of bias. Most of the studies were high risk due to the absence of blinding personnel and participants. This lack of blinding could affect the outcomes of the studies (Figure 3).

Interventions and Their Effectiveness

Physical Interventions

Physical interventions were the most investigated approach observed among the included studies. A total of 46 studies

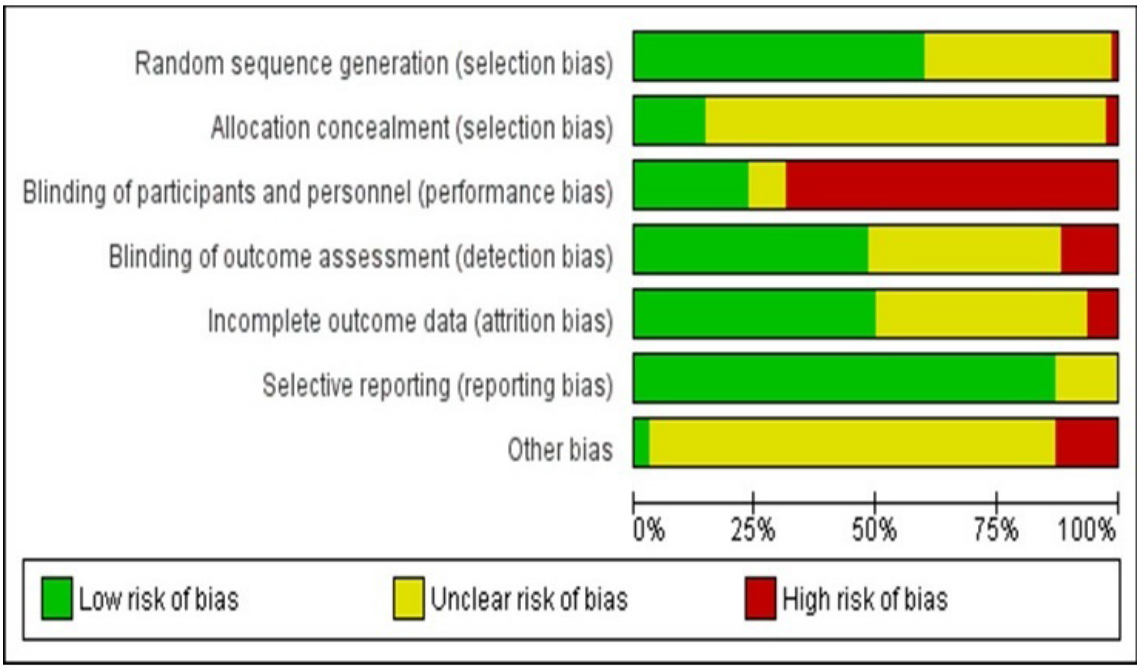

Figure 3: Summary of Risk of Bias.

Table 1: PICOT Table of Included Studies.

Category	Description
Population	Adult patients suffering from peripheral arterial disease
Intervention	Any complementary & alternate intervention approved according to guidelines and mentioned in the studies that meet the inclusion criteria of this study
Control	Any placebo or comparator eligible for inclusion in this study
Outcome	Improvement in Physical Wellbeing and Vascular function
Time	Inception to 30st April 2022

included in this review evaluated the effectiveness of physical interventions i.e.,.[31,32,34,37,38,40-42,44-47,49,51,53,55,57-59,61,62,65,66,68-75,77,78,82-84,87-90,92,93, 98,100,102,104] The various forms of exercises evaluated were Supervised Exercise Training program (SET), treadmill training program, home-based exercise program, simple walking, resistance training performed with and without loads, special exercises for calf muscles or lower limbs, Nordic Pole Walking (NPW) and strength training for the whole body. Each of these trials had a different duration of interventions and outcomes. Most of the studies compared exercise intervention with a control group having moderate physical activity in form of stretching or walking or no physical activity. Some studies compared one form of exercise intervention with another form of exercise intervention and others compared similar exercise interventions but with slightly different intensities.

The majority of trials[34,41,47,51,53,55,62,71,78,83,89,90,92,93] stated the use of SET or simply exercise training to estimate its impact on the PAD or associated/ defined parameters. However, one of the main issues that were noticed that there was no protocol based on which SET or any other exercise interventions was standardized. It was observed that all type of exercises showed improvements in 6 min Walking Time (6-MWT), Mean Walking Distance (MWD), vascular functions, and health-related Quality of Life (QoL) in contrast to control group. Also, many studies suggested incorporating physical activity into the daily life routine of PAD patients is found to be an effective measure in improvement the overall wellbeing improvement in the symptoms associated with the PAD. In addition, study by Correia, M *et al.*, (2022)[104] compared the isometric handgrip training with a control group of sham training. The intervention group showed improvement in brachial BP and vascular functions, but no improvement was observed in arterial stiffness.

In few studies, home-based walking behavior change was compared with the control group.[40] In addition, improvement in average walking speed and QoL was observed in the intervention group.[45] Improvement in these parameters was observed however, the clinical efficacy is yet to determine versus pharmacological intervention.[32] In some of the studies pharmacological interventions were compared exercise and rehabilitation with 6 hr of Iloprost Infusion OD for 2 weeks. The results showed that Pain-Free Walking Distance (PWFD) was significantly improved in the exercise group as compared to the pharmacological

intervention. While[59] compared to normal medical treatment as intervention and normal medical treatment with Supervised Exercise (SE) showed the improved walking capacity, improved QoL, and reduced body fat as compared to the control group. Another study compared the Optimal Medical Care (OMC), OMC and SE.[69] The OMC and SE showed significant results in walking time as compared to the other two intervention groups. The effects of resistance training in comparison to control,[49,98] was also compared, and showed positive effects on cardiovascular function and proposed resistance training to be an alternative option that can decrease the cardiovascular risk of PAD patients. In addition, High-intensity Resistance Training (H-RT) and Low-intensity Resistance Training (L-RT) were compared with the control group in[75] however, no improvement in L-RT and control group was observed, but H-RT improved the 6-MWT. Another intervention that was utilized to improve the vascular function of the PAD patients was video instructions along with an online home-based interactive sedentary reduction program.[58] Results have shown that there was a significant improvement in 6-MWT and vascular function in the intervention group.

Various forms of exercise were studied in five clinical trials. Low and high-intensity exercise groups were compared with the control group of having educational sessions only for 48 weeks.[65] There was a significant improvement in 6-MWT in high-intensity exercise as compared to other groups. Conventional and modified exercises were practiced for 12 weeks, and both groups showed improvement in muscle metabolism but no improvement in walk distance, walking economy, and deoxygenation rate.[68] Oxygen-guided intervention versus traditional pain-based exercise was also compared for its effectiveness among PAD patients. Improved in walking capacity and mitochondrial capacity in the intervention group was observed in comparison with the control group.[70] Home-based guided exercise vs standard exercise without guidance was also tested and it reported a significant improvement in the number of steps count and QoL in the guided exercise program.[72] Heated Water Exercise Therapy (HWET) was compared with Land-Based Exercise Therapy (LBET). The HWET reduced the arterial stiffness, BP and resting HR, and improved Claudication Onset Distance (COD), walking distance and muscular strength more effectively than LBET.[74]

The exercise was compared with surgical treatment options like angioplasty or revascularization in three studies. After the intervention, outcomes were improved in all three of them; however, the surgery group provided slightly better and more immediate results in comparison to the exercise alone group and these studies also recommended conducting larger RCTs to confirm the results[44,57,82] On the other hand, in[61] the combined supervised exercise program and angioplasty showed better results than exercise and angioplasty alone. Calf raising exercise was compared with the control group of traditional walking exercise in,[87] and the results showed a significant improvement in PWFD, MWD, and QoL in the intervention group, while no improvement was reported in mitochondrial capacity and peak oxygen uptake. Nordic Pole Walking (NPW) was compared with simple treadmill training and simple walking in two clinical trials. Both trials recommended that NPW is equally effective as simple treadmill training and simple walking and additionally NPW produced more rapid results by decreasing walking pain and enhancing the overall cardiac fitness of patients.[37,100] Similarly, strength training was proved to be more beneficial than simple walking as it decreased pain endured by PAD patients while walking.[77]

Aquatic walking training was compared with the control group of no exercise. There was a significant improvement in arterial stiffness, exercise tolerance, and physical functions in the intervention group only.[73] In few studies, it was noted that treadmill training with either 40% or 80% of maximum exercise capacity had similar effects on the walking performance of patients with IC.[46] The same was the case in another trial which compared a single bout of resistance exercise with and without load and showed that both groups had decreased blood pressure variability and cardiac load.[102] In the other two studies, treadmill training was compared with no physical activity and showed better results in the intervention groups i.e., improved walking capacity, Pain-Free Walking Time (PFWT), calf muscle strength and Mean Walking Time (MWT).[66,88]

Simple walking training was compared with a control group performing stretching only in some studies.[31,42] It was found that patients of the walking group had improved total distance walked along with the increment in pain onset walking distance. Walking training also enabled patients with PAD to perform the exercise with some tolerable pain. A unique study performed a comparative analysis of the combination of three different exercises at three different points on lower limbs and the placebo group having disconnected electrotherapy equipment. Various blood parameters and flow velocity of blood were enhanced following the exercise protocol were assessed. The authors of the study also implied that this exercise protocol could be a useful tool to decrease the progression of PAD in type 2 diabetic patients [38]. Plantar flexion device and standard care were compared with the control group of standard care only. No evidence regarding the efficacy of the device was reported.[84]

Oral Supplements

Fifteen studies included in this review evaluated the effectiveness of various oral supplements either alone or in combination, with or without control group.[35,36,48,50,56,63,76,79,80,85,91,96,99,101,105] The oral supplements included: nitrate, L-arginine and prostaglandin, *Gingko biloba* extract, Poly Unsaturated Fatty Acids (PUFAs), resveratrol, flavanol-rich cocoa, MitoQ, and Annurca apple polyphenolic extract. Multiple studies were performed on PUFAs, *Gingko biloba* extract, and nitrates. Two studies compared

different interventions, one study compared two intervention groups with a control group, two studies compared intervention groups with a control group, and the rest of ten studies compared intervention with a placebo group.

Ginkgo biloba Extract (EGb 761)

Two studies provided evidence of the use of *Ginkgo biloba* extract (EGb 761). However, the results of both studies are inconsistent as 300 mg/day dose caused a very slight but insignificant increase in the outcome of treadmill walking and flow-mediated dilation when compared with placebo[48] whereas 240 mg/day (higher dose) caused more improvement in walking distance in comparison to a low dose of 120 mg/day of EGb 761[80].

Poly Unsaturated Fatty Acids Supplementation (PUFA)

Four studies[50,76,79,99] evaluated the effects of PUFAs on various inflammatory biomarkers, endothelial function, and serum triglycerides. All these studies suggested that PUFA supplementation in form of fish oil did not cause any effect on markers of inflammation while somehow the flow-mediated dilation and serum triglycerides production was increased in patients with PAD.

Annurca Apple Polyphenolic Extract

Only one clinical trial extending up to 24 weeks estimated the effect of Annurca apple polyphenolic extract. Polyphenolic extract was found to be safe and found to be an effective natural therapy to relieve the symptoms associated with PAD in comparison to placebo.[85]

Resveratrol

Comparison of the effects of two doses i.e., 125 mg and 200 mg of Resveratrol in contrast to placebo in older PAD patients was found to be insignificant in generating a substantial evidence or improvement among PAD patients.[105]

Nitrates (NO_3)

Four clinical trials report the results on the nitrate supplementation among PAD patients. One study was performed for 180 minutes with orange juice in the control group and resulted in increased peripheral tissue oxygenation and exercise tolerance.[96] The other three compared $NaNO_3$ supplementation with placebo and resulted in significant improvement in 6-MWD and blood flow in the intervention group.[35,56,91]

L-arginine and Prostaglandin

Comparison of the interventions; L-arginine and exercise, prostaglandin and exercise with the control group of exercise.[36] showed a significant improvement in PFWD and Absolute Walking Distance (AWD) in both intervention groups.

Flavanol-Rich Cocoa

Flavanol-rich cocoa was compared with placebo and the outcomes were significantly better in the intervention group i.e., 6-MWD and mitochondrial COX activity as compared to the placebo.[63]

MitoQ

MitoQ 80mg was administered for 12 weeks, and it improved endothelial function significantly without affecting Blood Pressure (BP), Heart Rate (HR), and arterial stiffness among the PAD patients.[101]

Miscellaneous Interventions

Sixteen clinical trials evaluated the effects of other interventions in treatment of PAD.[27-30,33,39,43,52,54,67,81,86,94,95,97,103]. These studies included the electrical or electromagnetic field stimulation, GaAlAs Laser Acupuncture, Remote Ischemic Preconditioning (RIPC), heat therapy, Extracorporeal Shock-Wave Therapy (ESWT), vibration therapy, T'ai Chi Chuan Exercise, intermittent mechanical compression, intermittent negative pressure, Waon therapy, cardiac rehabilitation programs, and chelation therapy. Results have shown that across majority of the trials, intervention group was found to be significantly improving the function and Qol among the PAD patients.

Pulsed Electromagnetic Field (PEMF) Therapy

PEMF along with pharmacological and dietary (P and D) supplementation was compared with P and D supplementation as a control group. The graded exercise test (GXT) and ABI was found to be significantly improved in the intervention group as compared to the control group.[27]

GaAlAs Laser Acupuncture

GaAlAs laser acupuncture and pharmacological therapy vs control group with pharmacological therapy only was also tested for its effectiveness among PAD patients.[28] The results demonstrated that there was a significant improvement in 6-MWD in the intervention group as compared to the control group.

Neuromuscular Electrical Stimulation (NMES)

NMES and supervised exercise program (SEM) were compared with SEM only. The results showed significant improvement in intermittent claudication distance and maximum claudication distance in the intervention group as compared to the control group.[33]

Ethylenediamine Tetra Acetic Acid (EDTA) Chelation therapy

Intravenous infusion of EDTA in PAD was also investigated. However, the results demonstrated that EDTA infusion in comparison to placebo was not very successful to improve

outcomes like walking distance, vascular parameters, and health-related and general quality of life.[86]

Tai Chi Chuan (TCC)

Tai Chi Chuan is a form of traditional Chinese martial arts exercise. It contains a combination of breathing exercises with various body postures whereas the transitions between various postures are slow, smooth, and calm. A 30 min session of TCC decreased the acute systolic blood pressure but caused no effect on heart rate. Also, the study suggested that this TCC exercise session could be used as an alternative treatment option for PAD patients to reduce the vascular load.[95]

Intermittent Mechanical Compression (IMC) Device

Impact of IMC devices on claudication distance and ABI was also explored. It stated that the use of IMC devices for 3 months in PAD patients could be useful because it caused an increase in PFWD covered by PAD patients and also improved the post-exercise ABI results.[43]

Vibration Therapy (VT)

Vibration therapy was compared with no vibration therapy in the control group and resulted in improved 6-MWT in the intervention group only.[94]

Connective Tissue Reflex Massage

Massage therapy was done to observe the efficacy of connective tissue reflex massage on limbs of people suffering from PAD and it expressed that 15 week of this massage improved blood flow and vessel dilations in a lower limb when compared with placebo.[39]

Remote Ischemic Pre-Conditioning (RIC)

RIC i.e., inflating a blood pressure cuff to cause ischemia and then allowing reperfusion was another measure that was investigated for its effectiveness among PAD patients. The results showed improvements in the blood flow of limbs equivalent to supervised exercise training. Also, when RIC was combined with exercise in other groups there was no added benefit. However, the authors of the study recommended the need for larger RCTs to confirm the findings.[29]

Transcutaneous Electrical Nerve Stimulation (TENS)

Result of a clinical trial testing the effect of 45 minutes session[97] of electrical nerve stimulation improved walking distance and reduced pain in the limbs of patients. However, the sample size was not sufficient power to support the facts and may need larger sample to support this claim nonetheless the results need further verification with larger RCT.

Extracorporeal Shockwave Therapy (ESWT)

ESWT was compared with Sham treatment as a control group and resulted in significant improvement in MWD and cardiac function in the intervention group as compared to the control group.[52]

Intermittent Negative Pressure (INP)

Comparison of the intervention of 40 mmHg INP with the control group of 10 mmHg INP was also investigated in one clinical trial.[54] The results showed a significant improvement in PFWD and MWD and no improvement in ABI and Ischemic blood flow in the intervention group.

Heat Therapy

Heat therapy or spa bath was compared with traditional exercise therapy in two clinical trials. PFWD and MWD of the patient were increased after intervention in both groups. both studies recommended that the treatment with heat may be a useful therapy for PAD patients.[30] Another clinical trial tested the impact of heat therapy at 48°C with the control group at 33°C and resulted in an improvement in physical functions in the intervention group only.[67]

Waon Therapy

Waon therapy was compared with conventional therapy. Significant improvement was observed in 6-MWD and ABI in the intervention group as compared to the control group.[81]

Cardiovascular (CV) Rehabilitation Program

The CV rehab program and usual care without rehab were compared and insignificant results were found on the criteria of PWFD and MWD in the intervention group.[103]

Quantitative analysis

As described in the method section our intentions were to perform meta-analysis so that effect of each intervention can be estimated to draw a better conclusion. However, upon extraction it was revealed that only seventeen studies have described the base and endpoint quantitative data. The remaining n=60 studies have either reported the statistical interpretation/ values that are generated after statistical analysis and using these statistical values statistical amputations were not possible to generate a value which can be utilized to perform meta-analysis. Demonstrated that all the interventions i.e. physical methods, supplements and miscellaneous methods that were evaluated in the clinical trials were found to have a positive impact of the clinical parameters of the PAD patients. Exercise therapy trials conducted by Woessner *et al.* (2018)[91], Wang *et al.* (2009)[90], Wang *et al.* (2006)[88], McDermott *et al.* (2021)[65], was found to be significantly improve the walking time, quality of life and oxygen saturation level. Bock *et al.* (2018), [35] Kruse *et al.* (2018)[56] investigated the impact of NaNO3 among PAD patients. It was observed that there was significant increase in the 6 MWD when the data was compared to the baseline values in comparison to the control/ placebo group. Similarly, there was a significant increase in the plasma nitrate level which

assisted in improving the calf blood flow. Böger *et al.* (1998)[36] investigated the impact of 8 g L-arginine BD+Exercise versus 40 mcg Prostaglandin E1 (PGE1) BD+Exercise. A significant increase in the PFWD and AWD was observed in both groups. However, the percentage improvement from baseline to the endpoint was highest in the Prostaglandin E1 (PGE1) group. As exercise was incorporated in both groups therefore it was challenging to estimate the true effect of the PGE1 versus L-arginine. Wang *et al.* (2007)[89] and Gardner *et al.* (2008)[48] investigated the effect of *Gingko biloba*. It was observed that Gingko biloba alone and in combination with the exercise therapy has resulted in an increase in MWT, PWFT, Peak Oxygen consumption and resulted in decline in blood viscosity. Moreover, results from the trial of Gardner *et al.* (2008)[48] reported an increase in QoL life from base line showed improvement in WIQ speed, distance and stairs. In addition, to the parameters explored by the trials in physical and other interventions. Use of fish oil was noticed to have substantially increased flow mediated vasodilation and decline in the effect on inflammatory biomarkers was better in comparison to the control/ placebo group Grenon *et al.* (2015)[50] and Ramirez *et al.* (2019).[76]

DISCUSSION

Peripheral Arterial Disease (PAD) is the process of narrowing of lower limb arteries due to atherosclerosis and is associated with high cardiovascular morbidity and mortality. It also causes a huge economic and humanistic burden on society.[106] A broad range of therapeutic and endovascular treatment options are available for PAD which are effective and safe however many complementary and alternative medicine therapies are also in practice hence the focus of this study was to evaluate the efficacy of various CAM for the management of PAD.

This review has shed light on the various physical/ exercise therapies, complementary and alternative therapies that have shown some effectiveness in the disease under study. All these therapies have been broadly classified into physical therapies, which include some form of exercise, oral supplements, and miscellaneous therapies which did not fall in the first two categories. The data extraction insinuated improvement in at least one or more primary outcomes except for 8 studies[34,48-50,54,84,86,99] which reported no significant improvement. All the studies reported at least one of the primary outcomes listed in except 2 studies that reported inflammatory biomarkers[31,99] and pulse wave velocity, plasma vWF and platelet aggregation.[99] Quality of life was assessed by various studies and various tools were used to quantify the results. These tools included Walking Impairment Questionnaire (WIQ),[40,46,48,50,51,62,65,71,72,76,78] Medical Outcomes Study Short Form Health Survey (SF-36),[40,44,45,48,51,55,57,61,62,65,71,78,82,87] Edinburgh Claudication Questionnaire (ECQ),[28] Vascular QoL (VascuQoL) Questionnaire,[44,61,72,82] Health Utilities Index,[46] Intermittent Claudication Questionnaire (ICQ).[51] Self-Efficacy for Physical Activity (SEPA) Questionnaire[72] and European Quality of Life Visual Analog Scale (EQ-VAS).[78]

In majority of the studies physical intervention/exercise therapy was utilized as one of the main regimens to improve the physical, mental, and biological wellbeing of the PAD patients. Regardless of the risk of bias, it could be postulated that physical intervention to be considered as one of the first line non-pharmacological approaches for the management of PAD. In addition, another important fact that was revealed from this review is the effect of supplements in improving the plasma oxygen level, vasodilation of the vessels and improvement in the physical tasks. These include nitrate, either in the form of $NaNO_3$[35,56] or in the form of beetroot juice,[91,96] *Gingko biloba*, in different doses[80] or compared to placebo[48] or in combination with exercise[89] and fish oil compared with placebo.[50,76] Some studies reported various side effects due to the use of oral supplements[99] for example belching, heartburn, nosebleeds, nausea, vomiting and diarrhea with the administration of some PUFAs due to which 12 people withdrew from the study.[64] Diarrhea and abdominal pain due to resveratrol administration but these resolved spontaneously, and abdominal pain was reported by[76] due to fish oil but it did not affect the study.

Based on the evidence of this review; it was clear that physical therapy in form of exercise was greatly beneficial for patients with PAD. It improved patients' quality of life and increased their walking ability. Similar beneficial effects of exercise on PAD patients were reported by[105,107] Many studies included in this review commented that clinicians should recommend PAD patients incorporate physical activity in their daily routine and such recommendations are also available in NICE guidelines.[108] Although all forms of physical activities showed promising results; however it is not clear which type of exercise/ physical therapy will be or which duration of physical activity is most efficacious among all of them.[109] defining these criteria's will be beneficial for not only clinical but also for the patients as well. Nature, type, and duration of physical interventions will assist the patient to devise self-care schedule which will assist in improving their overall wellbeing. Such issues should be addressed in future clinical trials that specifically focusing on optimizing the duration of exercise regimens effective for PAD in long term.[110]

Furthermore, this review also revealed the efficacy of nitrate supplementation as a treatment option for patients with PAD. Nitrate supplementation either as $NaNO_3$ or beetroot juice significantly improved the walking distance and vascular function of the PAD patients and quantitative evidence has proven the use of nitrate in the management of PAD.[111] Similarly *Ginkgo biloba* extract was also observed to be significantly improving the vascular function and decreasing the blood viscosity[112] thus assisting the patients with PAD with or without claudication.[113]

Most studies have shown the CAM therapies to be efficacious and possible alternatives to the pharmacological intervention

used at present. However, it is still a bit difficult to recommend the said CAM therapies because it is difficult to conclude which therapy is the best. Furthermore, several discrepancies were seen in the outcomes due to which the results of trials could not be compared and therefore meta-analysis could not be performed. The reason for failure to compare included: a) different duration of treatments, b) no standard comparator, c) absence of dose standardization of various supplements, d) different sample size and e) different endpoints of the studies. Therefore, it would be wise to exercise caution in the use of these therapies until they are approved by FDA or WHO.

Apart from pharmacological interventions, surgical interventions (e.g., endovascular revascularization) are also frequently used treatment options for patients with PAD.[114] Therefore, it is also needed to compare the efficacy of CAM therapies with these surgical interventions and other pharmacological interventions. All current and future trials should follow the CONSORT guidelines[115] and the said trials should be comprehensive.

In clinical perspective this review suggested strong evidence for the use of exercise-based interventions and use of certain supplements i.e. nitrates and *Ginkgo biloba* as an effective measure for the effective management of PAD. Clinical guidelines should consider recommending the use exercise and supplements as a non-pharmacological measure to improve the wellbeing of the PAD patients. Moreover, there is a need to establish a consensus regarding the duration, type and timing of the exercises and the dose of supplement which may delay the progression of PAD and improve the biological function and systematic parameters among PAD. Another important issue that should be kept under consideration is the moderate to low quality of studies that were included in this review performance and selection bias were the two main issues which warrant the clinicians to carefully decide on the selection of the physical and CAM therapies for PAD patients.

CONCLUSION

This review suggests a positive impact of physical activity on peripheral arterial disease patients' quality of life. Evidence also shows that Physical activity/ exercise-based intervention alone or in combination with the supplement are found to be effective among PAD patients and shown significant results in intermittent claudication. Parameters which were found to be improved among PAD patients were PFWD/ Time, CD, ICD, AWD, MWD, QoL and plasma oxygen saturation. However, to decide more precisely regarding the type of interventions that should be added for PAD patients, clinical well designed randomized clinical trials are needed to confirm these findings. In addition, there was a huge variety of treatments that were compared across the selected studies with different assessment parameters. Unfortunately, this massive diversity in dose, duration and frequency of supplementation and variation in the assessment parameters has limited the option for a quantitative comparison. This indicates the need of methodologically well-planned high quality clinical trials so that CAM intervention can be included in the standard treatment protocol of the PAD patients.

STRENGTHS AND LIMITATIONS

This review is perhaps the first comprehensive effort to evaluate and compare the efficacy of different physical/exercise based and CAM therapies. Adoption of the recommended PRISMA and Cochrane to generate the body of evidence across the diverse database is one of the main strengths of this review. In addition, PICOT framework assisted in generating a very specific level of evidence for the selected outcome and objectives. However, in most of the systematic reviews the reliance of the conclusion is on the published literature. There was a huge diversity of regimens and assessment tools that were utilized across the selected studies in this systematic review therefore a qualitative analysis was not possible due to lack of similarities among the included studies. Therefore, meta-analysis was not possible.

Nonetheless, the conclusions made by this review could be restricted in terms of its scope because as mentioned in the eligibility criteria only studies published in the English language were included. This language barrier might have caused the exclusion of many relevant and useful RCTs as they were not available in the English language.

CLINICAL RECOMMENDATION

The positive impact of physical/ exercise based, and CAM therapies seen in this review creates a need for future research. Future clinical trials should include larger significant sample size and blinding where possible. This would help plan a better pharmacotherapy, therefore, improving the outcomes of the disease. Any future review should incorporate a meta-analysis using a standard comparator to quantify the effectiveness of these physical/exercise based and CAM therapies and therefore improve the evidence of their effectiveness.

Author Contributions

Yazeed Saud Alanizi and Wala'a Mohammed Al-Sulais: Conceptualization, methodology, software, data curation, validation, formal analysis, investigation, resources, writing, visualization, and funding acquisition. **Ahad Aref Alsulays and Nashi Dukhi Albaqami:** Investigation, resources, writing, visualization, and funding acquisition **Abdulaziz Khalaf Alshammari and Mujtaba Abbas Jasim Aljasim:** Investigation, resources, writing, visualization, and funding acquisition. **Ahad Aref Alsulays and Nashi Dukhi Albaqami:** Investigation, resources, writing, visualization, and funding acquisition. **Bashayr Abdullah Alanzi and Abdullah Ayed Alshammari:** Investigation, resources, writing, visualization, and funding acquisition. **Hanan Haif Alshammari and Hadeel**

Saad Althagafi: Investigation, resources, writing, visualization, and funding acquisition. **Khansa Hamza Hussain and Maali Ramadan ALshammari:** Conceptualization, methodology, software, data curation, validation, formal analysis, resources, writing, visualization, supervision, and project administration. **Mohammed Kanan Alshammari:** Conceptualization, methodology, software, data curation, validation, formal analysis, resources, writing, visualization, supervision, and project administration.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ABI: Ankle Brachial Index; **6-MWD:** 6-Minute Walking Distance; **PWFD/T:** Pain-Free Walking Distance/Time; **CD:** Claudication Distance; **ICD:** Initial Claudication Distance; **MCD:** Maximum Claudication Distance; **AWD:** Absolute Walking Distance; **MWD/T:** Maximum Walking Distance/Time; **COT:** Claudication Onset Time; **TWD:** Total Walking Distance; **QoL:** Quality of Life; **BP:** Blood Pressure; **WIQ:** Walking Impairment Questionnaire.

SUMMARY

The quality of life of patients with peripheral vascular disease was shown to be positively impacted by physical activity, according to the final evaluation. Furthermore, it was shown that nitrate and ginkgo biloba supplementation worked well for individuals with PAD and intermittent claudication (IC). According to this review, physical exercise improves the quality of life for those with peripheral arterial disease. Additionally, research indicates that supplementation with physical activity or exercise-based intervention is beneficial for PAD patients and has a notable impact on intermittent claudication.

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