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Angiotico-1: A versatile drug in electrohomeopathy system of medicine is an arterial specific remedy substantially uses for peripheral arterial disease (PAD): An extensive review

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Abstract
Peripheral arterial disease (PAD) is atherosclerosis or hardening of the arteries, is a mess that occurs in the arteries. Medications suggest to treat conditions such as anti- hypertensives like vasodilators or ACE inhibitors, anti- cholesterols like statins and antiplatelets like clopidogrel or aspirin. The management of the disease includes diabetic management, stress management and pain management to be aided. Phytochemicals produced by plants have been widely studied for their potential health effects and role in various diseases including PAD. In this review, we focus on PAD and discuss the evidence related to the clinical utility of Angiotico-1, an Electrohomeopathy system of herbal medicine which is capable of exerting similar medication and management action as modern medicines for the treatment as well as management of PAD. We also highlight the herbs present in Angiotico-1 responsible for the functional outcome of Angiotico-1 on PAD.

Keywords: Angiotico – 1. electrohomeopathy, peripheral arterial disease

1. Introduction
Arterial disease is a vascular disease that affects the arteries of the body. As arteries are extensively present in almost all parts of the body, diseases of the arteries can affect any part of it. The arterial disease includes Peripheral arterial disease, Abdominal aortic aneurysm, Thoracic aortic aneurysm, Coronary artery disease, Carotid artery disease, Vertebrobasilar disease, Renal vascular disease, Thoracic outlet syndrome etc. Peripheral Arterial Disease (PAD) is an arterial disease where plaque builds up in the arteries causing the restriction of blood flow to the upper and lower extremities. To control the disease progression, physicians either opt for non-invasive vascular treatment or invasive vascular treatment depending upon the intensity of disease. Signs and symptoms of PAD can differ from mild to severe. These symptoms are due to restricted oxygenated blood to the leg(s) or arm(s). More advanced symptoms can include pain in the lower extremity with restricted function, coldness or discoloration of the extremity, and slow healing sores or gangrene. Eventually due to lack of adequate blood supply, tissue damage may occur leading to open sores which may further progress to gangrene. Conservative management therapy or aggressive treatment methods options but the purpose is to minimize cardiovascular mortality as well as to refine the quality of life in severe claudication and to restrict the chance of amputation in patients. Other strands of conservative management include handling of concurrent medical conditions such as: diabetes mellitus, high-cholesterol, hypertension, stress and pain. As part of conservative management regimen, antiplatelet therapy may be prescribed [1, 2]. Alternative therapy including Ayurved, Homeopathy, Electrohomeopathy, Unani, Yoga, Chinese medicine. These playas an important role to counter the progress as well as management of PAD.

1.1 Alternative Electrohomeopathy therapy
In 1865, an Italian Scholar Count Cesare Mattie derived a new system of herbal medicine and nominated as Electrohomeopathy. The ethics of Count Mattie was that an individual is constituted as a complex one and any of his disease can only be cured by the use of complex remedies. These complex remedies could restore the deviated physiological function of different organs and biochemical constituents into its original position. So Count Cesare Mattie postulated the concept of Electrohomeopathy is "Complexia Complexes Curantor" [3]. Angiotico-1 or A-1 belongs to the blood remedy league of Electrohomeopathy system of medicine and is considered as arterial specific remedy. A-1 comprises spagyric essences of different plant combinations like *Arnica montana*, *Avena sativa*, *Capsella bursa-pastoris*, *Hydrastis canadensis* and *Sanguinaria canadensis* [4].

It is comprehensively used by local practitioners to treat almost all kinds of peripheral arterial disorders.

2. Methodology

In the initial phase, an extensive literature search was accomplished in the following databases: Google Scholar, Science Direct, PubMed Central, Elsevier, Springer Link and many others. The keyword used was the role of the *Arnica montana*, *Avena sativa*, *Capsella bursa-pastoris*, *Hydrastis canadensis* and *Sanguinaria canadensis* (separately) in PAD. All the hits secured when searching the database using the above search criteria were assembled, and repeated articles were deleted. The articles were scrutinized by reading the full text for the following information: Phytochemical properties, pharmacological properties, and ethno- pharmacological data of above medicinal plants on PAD. In the final step, to obtain more data, a manual search was performed using the reference list of the included articles.

2.1 Phytochemical constituents and pharmacological activity of *Arnica montana* in PAD

2.1.1 Phytochemical constituent: *Arnica montana* a herbal plant that is a chief component of Angiotico-1, possesses almost all qualities to treat PAD. The main constituents of *Arnica montana* are essential oils, fatty acids, thymol, pseudoguaianolide sesquiterpene lactones and flavanone glycosides [5].

2.1.2 Pharmacological activity: The pharmacological activity of *Arnica montana* has been presented in Table-1.

Table 1: Pharmacological activity of *Arnica montana* with description and reference

Pharmacological activity	Description	Reference
Cardio protective	It is a cardio protective and is used to treat as well as prevent coronary disease.	[6]
Improves respiration	It is also reported to increases respiration frequency and volume by 35 and 43%, respectively, in rats and rabbits when injected	[7]
Improves blood circulation	*Arnica montana* is reported to improve blood circulation to relieve symptoms of diseases relating to the restricted blood flow to nerve endings and the limbs of patients and reflex sympathetic dystrophy syndrome, which includes fibromyalgia, toxic neuropathy and diabetic neuropathy.	[8]
Anxiolytic	Ahmed *et al*. evaluated various neuropharmacological screening tests and found that *Arnica montana* decreased the exploratory activity and locomotor activity in mice and mice spent more time in light compartment and therefore had anxiolytic effect.	[9]
Anti oxidant	*Arnica montana* shows Mitochondrial oxidative stress induced by $Ca(^{2+})$ plus inorganic phosphate and or $Fe(^{2+})$ citrate mediated lipid peroxidation through changes in oxygen consumption.	[10]
Analgesic	*Arnica montana* is widely used for treatment and prevention of pain and bruising.	[11]
Antihaemorrhagic	*Arnica montana* shows antihemorrhagic effect on postpartum blood loss	[12]
Antiplatelet activity	Pawlaczyk *et al*. in 2009 found that hexuronic acids and phenolic glycoconjugates present in *Arnica montana* are responsible for the anticoagulant activity of the plant	[13]

2.2 Phytochemical constituents and pharmacological activity of *Avena sativa* in PAD

2.2.1 Phytochemical constituents: The chief phytoconstituents reported from *Avena sativa* are alkaloids, carbohydrates, flavonoids, sterols, proteins, lipids and saponins [14].

2.2.2 Pharmacological activity: The pharmacological activity of *Avena sativa* has been presented in Table-2.

Table 2: Pharmacological activity of *Avena sativa* with description and reference

Pharmacological activity	Description	Reference
Antioxidant	Avenanthramides present in *Avena sativa* are bioavailable and have antioxidant activity in humans.	[15]
Cardio protective	It has been reported the ACE inhibiting property of *Avena sativa*.	[16]
	Avena sativa also possesses vasodilatory effects.	[17]
Anti-inflammatory	Avenanthramides, a phytocostituent of *Avena sativa* has been used as lipoxygenase inhibitors.	[18]
Antidepressant	*Avena sativa* exerts an antidepressant effect in animal models. The flavonoid components of MSEAS might be interacting with an adrenergic system in mediating the anti- depressant effect of *Avena sativa*.	[19]
Hypolipidemic activity	*Avena Sativa* exerts Anti-atherosclerotic Effects on blood vessels of Albino rats has been proved.	[20]

2.3 Phytochemical constituents and role of *Capsella bursa-pastoris* in PAD

2.3.1 Phytochemical constituents: The plant contains polypeptides, flavonoids, choline, acetylcholine, histamine and Tyramine along with minerals, vitamin A, ascorbic acid, proteins, linoleic acid and omega -3 polyunsaturated fatty acid [21].

2.3.2 Pharmacological activity: The pharmacological activity of *Capsella bursa-pastoris* has been presented in Table-3.

Table 3: Pharmacological activity of *Capsella bursa-pastoris* with description and reference

Pharmacological activity	Description	Reference
Antimicrobial effects	Hasan RN et.al proved the Antibacterial activity of aqueous and alcoholic extracts of *Capsella bursa-pastoris* against selected pathogenic bacteria.	[22]
Anti-inflammatory	Joon Min Cha, et.al. proved the anti-inflammatory property of *Capsella bursa-pastoris* by estimating the amount of nitric oxide produced in lipopolysaccharide activated microglia cells.	[23]
Anti oxidant	Study of antioxidant activity of *Capsella bursa-pastoris* extracts stated that these extracts contain free radical scavengers. The extracts which contained many flavonoids exerted an antioxidant activity against	[24]

	DPPH radicals, peroxyl radicals, hydroxyl radicals, and hydrogen peroxide.	
Cardio protective	The plant increased coronary blood flow in dogs following intra-arterial administration, and caused a slight inhibitory effect on ouabain-induced ventricular fibrillation in the rat following intraperitoneal injection, together with a negative chronotropic effect.	[25]

2.4 Phytochemical constituents and role of *Hydrastis canadensis* in PAD

2.4.1 Phytochemical constituents: Bioactive chemical constituents of the plant *Hydrastis canadensis* is the plentiful sources of alkaloid phytochemicals (e.g. berberine, hydrastine and canadine, and lesser amounts of flavonoids (e.g. sideroxylin, 8-desmethyl-sideroxylen, 6-desmethyl-sideroxylin etcphenolic acids (e.g. neochlorogenic acid, chlorogenic acid etc.), sterol and other also present [26].

2.4.2 Pharmacological activity: The pharmacological activity of *Hydrastis canadensis* has been presented in Table-4.

Table 4: Pharmacological activity of *Hydrastis canadensis* with description and reference

Pharmacological activity	Description	Reference
Hypolipidemic activity	Several studies have demonstrated that the *Hydrastis canadensis* exhibited strong lipid lowering activity. Berberine effectively reduced total cholesterol, triglycerides and low-density lipoprotein.	[27]
Hypoglycemic activity	The insulin dependent response of *Hydrastis canadensis* may also be associated associate with the reverse state of diabetes, the hypoglycemia, with variable mechanisms and conditions. *Hydrastis canadensis* was found to have remarkable hypoglycemic effect, which was confirmed by the increase of insulin sensitivity and secretion, glucose absorption and metabolism.	. [28]
Anti-inflammatory activity	It was found that *Hydrastis canadensis* extract was able to modify lipopolysaccharide-stimulated macrophages responses such as reduction of TNF-α, IL-6, IL-10, and IL-12 production in a dose-dependent manner.	[29]
Anti-platelet aggregations	*Hydrastis canadensis* was also reported as a thrombin inhibitor and displayed an inhibitory property against thrombin-induced platelet aggregation.	[30]
Cardioprotective activity	Berberine, a phytocnstituent of *Hydrastis canadensis* also possesses Cardioprotective potential through its vasorelaxant effect. It blocks the release of intracellular Ca2+, accelerating endothelium-derived relaxing factor release and triggering of large-conductance Ca2+-activated K+ channel.	[31]
Anti oxidant	Berberine possesses antioxidant property which was confirmed in different radical scavenging models including DPPH radical, superoxide anion, radical scavenging assays etc.	[32]

2.5 Phytochemical constituents and pharmacological activity of *Sanguinaria canadensis*

2.5.1 Phytochemical constituents: *Sanguinaria canadensis* contains eight isoquinoline alkaloids at biologically relevant concentrations including six quaternary benzophenanthridine alkaloids (QBAs) sanguinarine, chelerythrine, sanguilutine, chelilutine, sanguirubine, chelirubine and two protopin alkaloids protopine and allocryptopine [33].

2.5.2 Pharmacological activity: The pharmacological activity of *Sanguinaria canadensis* has been presented in Table-5.

Table 5: Pharmacological activity of *Sanguinaria canadensis* with description and reference

Pharmacological activity	Description	Reference
Cardioprotective activity	It has been reported by Mackraj I. et.al. that *Sanguinaria canadensis* plays a crucial role in the regulation of blood pressure and cardiovascular function.	[34]
Anti-inflammatory activity	Xiaofeng Neu et.al.(2012) investigated the anti-inflammatory effects of sanguinarine and its modulation of inflammatory mediators from peritoneal macrophages,	[35]
Anti-platelet	Sanguinarine, alkaloid present in the root of *Sanguinaria canadensis* is a potent antiplatelet agent, which activates adenylate cyclase with cAMP production, inhibits platelet Ca^{2+} mobilization and TXA2 production as well as suppresses COX-2 enzyme activity.	[36]
Antimicrobial effects	*Sanguinaria canadensis* possesses potent antimicrobial properties.	[37]

3. Result and Discussion

The primary treatment goals in patients with PAD are to decrease cardiovascular morbidity and mortality and to improve limb-related symptoms (i.e., claudication) and quality of life [38]. Management of this condition may include endovascular repair, lifestyle improvement, disease management etc. The therapeutic approach to peripheral artery disease is composite and includes smoking cessation, adequate physical exercise, blood pressure regulation, cholesterol reduction and administration of antiplatelet and anticoagulants [39].

3.1 Lowering Cardiovascular Morbidity and Mortality

3.1.1 Hypolipidemic activity

Hyperlipidemia increases the risk of progressing PAD by 10% for every 10 mg/dL rise in total cholesterol [40]. Lipid lowering therapy like statins are used to get cholesterol-lowering effects. Statins are also used to improve walking distance and speed in patients with PAD.

Infected patients with PAD who used to take statins have been reported to have comparatively less annual decline in lower-extremity performance than those who did not use statins. Several studies have reported the effect of statins on claudication symptoms and proved that these molecules may have a modest effect at best for PAD [41].

Electrohomeopathy medicine Angiotico -1 also mimics the role of statins. A-1 contains *Avena sativa* and the phyto constituent present in *Avena sativa* possesses lipid lowering therapy [42, 43].

Another important constituent of A-1 is *Hydrastis canadensis* which also possesses **t**he hypolipidemic effect which in turn useful as lipid lowering therapy [44]. The hypolipidemic effect

of herbal constituents of A-1 also illustrated in Table-2 and Table – 4. Overall A-1 possesses an excellent hypolipidememic property and the property is highly essential for treatment as well as management for PAD patients and therefore the review justifies the use of A-1 for treatment and management for PAD.

3.1.2 Cardio protective and Hypertension Management

Many studies have shown a strong association between hypertension and PAD. As many as 50% to 92% of patients with PAD associated with hypertension [45]. Even though angiotensin-converting enzyme (ACE) inhibitors are considered the primary drug class of choice by some investigators, it is perhaps more important to treat to achieve goal to control blood pressure levels than to insist on a specific antihypertensive agent [46]. A-1 contains *Avena sativa* and possesses the quality of hypertension management [47]. Both of its ACE inhibitor capacity and vasodilatation capacity has already been reported in Table-2. Another component of A-1 *Capsella bursa pastoris* also helpful for lowering the elevated blood pressure [48]. *Hydrastis Canadensis* another important component of A-1 exerts its Cardio protective activity through its vasorelaxant effect by blocking the release of intracellular Ca^{2+}, stimulating endothelium-derived relaxing factor release and activation of large-conductance Ca^{2+}-activated K^{+} channel [49]. *Sanguinarine Canadensis* another important component of A-1 has been shown to block angiotensin II in a slow, nearly irreversible and non-competitive manner [50]. All most all the ingredients of A-1, has significant cardio protective effect [Table 1-5] and the cardio protective effect is an important aspect of management and treatment for PAD and thus the review divulges the use of A-1 for treatment and management PAD.

3.1.3 Antithrombotic Therapy

An antiplatelet medication such as aspirin or clopidogrel may be prescribed to reduce the risk of heart attack and stroke [51]. Antiplatelet agents such as aspirin are indicated for secondary prevention in high-risk cardiovascular patients. Although the benefits of aspirin in patients with CAD and carotid artery disease have been demonstrated by large-scale clinical trials [52]. Clopidogrel has been used as an alternative medication to aspirin in patients with PAD [53, 54]. *Arnica montana* and *Avena sativa* are the active constituents of A-1 and show significant antiplatelet activity [55, 56]. A-1 also have *Hydrastis canadensis* which was reported to be a direct inhibitor of thrombin, and showed an inhibitory potential (IC50 2.92 µM) against thrombin-induced platelet aggregation [57]. Antiplatelet effect of sanguinarine which is the phytoconstituent of *Sanguinarine Canadensis* is correlated to calcium mobilization, thromboxane and cAMP production and thus produce antiplatelet activity [58, 59]. More over the antiplatelet activity of *Arnica montana*, *Hydrastis canandensis Sanguinaria canadensis* has been illustrated in Table-1, Table-4 and Table -5 respectively. As the Antithrombotic therapy is an important aspect for treatment and management of PAD and the herbs present in A-1 are collectively able to manage it and therefore the review reveals the rationality of use of A-1 for treatment and management in PAD.

3.1.4 Pain management

Common Symptoms of PAD like Buttock, thigh, or calf pain with exertion (claudication), pain in legs and feet at rest, arm pain with exertion (PAD of arms). NSAIDs are usually administered for management of pain in PAD [60]. The *Arnica montana* of A-1 possesses significant analgesic and anti-inflammatory potential [61, 62] and can be an advantage for pain management. The anti inflammatory potential of *Avena sativa* helps to minimize inflammation and hence aids for pain management [63]. The anti inflammatory potentiality of *Hydrastis canadensis* also contributed for pain management [64]. Protopine an active constituent of *Sanguinaria canadensis* has been found to inhibit carrageenan-induced rat paw oedema with a potency three-fold higher than acetylsalicylic acid [65] and thus assists for pain management. Furthermore the analgesic and inflammatory properties of herbs of A-1 have been displayed in Table-1, Table-2, Table-3 and Table-5.Pain management is an important task for the treatment of PAD and the herbs present in A-1 individually or collectively capable of managing pain and therefore this review defends the use of A-1 for treatment and management in PAD.

3.1.5 Ulcer healing management

Ulcer on extremities that does not heal is an uncommon symptom of PAD. The primary aim to treat arterial ulcers is to increase blood circulation to the affected area, either by medically or surgically. Surgical options range from revascularization in order to restore normal blood flow to amputation and as for non-surgical measures, modifying contributing factors can slow or stop the progression of the local ischemia. Systemic use of antibiotics and dressing with antibacterial agents are the first line of choice to manage infection [66]. However as per the herbal medicine concern, Electrohomeopathic medicine A-1 plays an excellent role to minimize the infection as well as to promote wound healing. *Arnica montana* the constituent of A1 is very useful to increase blood flow at amputation area. (Table-1) and also to minimize the infection [67]. The minimum inhibitory concentration of *Capsella bursa pastoris* extracts was assessed by the twofold serial dilution method as described by Grosso C *et al*. [68]. This play a vital role for ulcer healing management. The antibacterial activity of *Avena sativa* was studied through evaluation of the minimal inhibitory concentration (MIC) in several studies including Rania EL Hosary *et al*. [69]. The extract of *Hydrastis candensis*. Proved the antibacterial activity against *Staphylococcus aureus*, *S. mutans*, *Streptococcus sanguis*, *S. pyogenes*, *Pseudomonas aeruginosa*, *Escherichia coli* and the activity were credited by the alkaloids berberine, canadine, and canadaline [70, 71]. *Sangunarea candensis* have significant antimicrobial action. When tested against 64 different oral microbial species [72]. Consequently all most all the constituent of A-1 [Table 1-5] possesses ulcer healing ability and therefore this review advocates for the use of A-1 for treatment and management in PAD.

3.1.6 Oxidative Stress management

Stress management is an important aspect of PAD [73]. A number of experiments conducted to prove the antioxidant therapy to control stress [74]. Glutathione, Polyphenol, Carotenoids, Dietary Minerals, Ascorbic Acid, Vitamin E, Ubiquinone Organosulfur Compounds etc are some of agents successfully used as antioxidants to prevent the oxidative stress and stress related compilations [75]. It was observed that the tannins and flavonoids present in *Arnica montana* extract decrease the exploratory activity and locomotor activity in mice and mice spent more time in the light compartment and therefore had an anxiolytic effect[76]. Iqra Riaz *et al*. proved the anti-oxidant potential of *Capsella bursa pastoris* which play a vital role for oxidative stress management, [77]. Anti-

depressant activity and Anxiolytic effect of *Avena sativa* has been proved by Usha Rani *et al*. & Kaur D *et al*., 2016. [78]. Thus from the above review it has been observed that the antioxidant ability of herbs of A-1 [Table1- 4] can play a vital role in treatment as well as management of PAD. For this reason this review discloses the justification for use of A-1 in treatment and management of PAD.

3.1.7 Diabetic management

Diabetes increases the risk of developing symptomatic and asymptomatic PAD by 1.5- to 4-fold and leads to an increased risk of cardiovascular events and early mortality [79]. Glycemic control is highly essential for the persons having PAD associated with diabetics [80]. Conventional antidiabetic medicines like Metformin, Sitagliptin, Canagliflozin, Glimepiride, Glipizide and Rosiglitazone as well as insulin is widely used to control diabetics.[81] An herbal plant *Hydrastis canadensis* is one of the important constituents of A-1 was found to have significant hypoglycemic effect, which was evidenced by the increase of insulin sensitivity and secretion, glucose absorption and metabolism[82]. Another herbal plant Avena sativa produces a significant decrease in blood glucose level which has been proved by Ahmed A. *et al*. [83]. Hence it was proved that the constituent of A-1 possesses ulcer healing ability and therefore this review vindicates for the use of A-1 in treatment and management of PAD.

4. Conclusion

The manifestations of PAD show a severe functional disability, which is considered to be the result of various pathophysiological mechanisms including skeletal muscle pathology, reduced nitric oxide bioavailability, oxidative stress, diabetics etc. The herbal constituents of Electrohomeopathy medicine A-1 collectively target these mechanisms and have a therapeutic effect for the treatment as well management of cardiovascular effect, thrombus, pain, ulcer healing, stress and diabetic in PAD patients. So the review reveals that it is quite justified to use Electrohomeopathy medicine Angiotico-1 in the treatment as well as management of PAD. However there are still a lot of studies required in this field which needs to be directed towards the molecular aspects of A-1 on this disease.

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