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Case Studies

Efficacy of Arjun (*Terminalia arjuna* (Roxb. ex DC.) Wight & Arn.) in Arterial Stiffness: A Case Report

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Abstract

Arterial stiffness is a growing epidemic associated with an increased risk of cardiovascular events. Arteriosclerosis means hardening of the arteries. Arterial stiffness or arteriosclerosis is often associated with but is distinct from atherosclerosis. High arterial stiffness is known to be a risk factor, as well as a prognostic marker for cardiovascular disease. *Terminalia arjuna* (Roxb.) Wight & Arn., an indigenous medicinal plant, has been proven to possess different cardioprotective properties, including positive inotropic, hypolipidemic, coronary vasodilatory, and antioxidant effects. A 40-year-old male presented to the outpatient department of Ajmal Khan Tibbiya College and Hospital in August 2022. The patient was diagnosed case of hypertension and type 2 diabetes mellitus and was taking medicines for the same regularly. His vitals and general physical and systemic examination were within normal limits at the time of interrogation, and all his baseline investigations, except his lipid profile, were within normal limits. The patient was screened for arterial stiffness, for which cardiovascular profile tests were performed on the patient using Diabetes Risk Profiler for the assessment of arterial health analysis, which showed severe arterial stiffness. After 12 weeks of treatment with the decoction of powder of *chāl arjun* (bark of *Terminalia arjuna*) 6 g twice daily, arterial health analysis assessment improved to mild arterial stiffness. The probable reason for improvement could be due to the *mufattiḥ sudad* (deobstruent), *muraqqiq-e-dam* (blood thinner), and *muqawwī-i-qalb* (cardiotonic) action of *chāl arjun*. This case report emphasizes and highlights the effect of *Terminalia arjuna* on arterial stiffness.

Keywords: Arterial stiffness; Diabetes Risk Profiler; *Terminalia arjuna*; Unani medicine; Case report

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Introduction

Arterial stiffness is a developing epidemic linked to a higher risk of cardiovascular events [1]. Arterial stiffness is defined as the decreased ability of an artery to expand and contract in response to pressure changes [2]. Arteriosclerosis means hardening of the arteries. It is a generic term reflecting arterial wall thickening and loss of elasticity [3]. It is a chronic pathological disease that refers to arterial lesions characterized by intimal thickening, stiffening, and remodeling of the arterial walls [4]. Three distinct types are recognized, each with different clinical and pathologic consequences: arteriolosclerosis, mönckeberg medial sclerosis, and atherosclerosis [3,4]. Arterial stiffness or arteriosclerosis is often associated with but is distinct from atherosclerosis [5]. Atherosclerosis increases the stiffness of major arteries. Increased intima-media thickening (IMT) represents one of the earliest stages of atherosclerosis [2]. Accelerated arterial stiffening has been linked to classic cardiovascular risk factors such as smoking, diabetes mellitus, high body mass index (BMI), and hyperlipidemia [2]. Arterial stiffness is also associated with early and asymptomatic impairment of systolic and diastolic myocardial function [6]. Arterial stiffness, measured by pulse wave velocity (PWV) and the ambulatory arterial stiffness index (AASI), is considered an independent predictor of cardiovascular mortality and morbidity in patients with cardiovascular disease and healthy individuals [7]. Many renowned Unani and Persian physicians like, *Jālīnūs, Abū Bakr Muḥammad ibn Zakariya Rāzī* (850 AD- 923 AD)*, ʻAli ibn ʻAbbas Al-Majūsī* (930 AD- 994 AD), *Ibn Sīnā* (980 AD-1037 AD), among others, have given the concept of *ṣalābat-i-nabḍ/ nabḍ ṣulb,* which can be correlated with the concept of arteriosclerosis (*taṣallub al-sharāyīn*) [8-13].

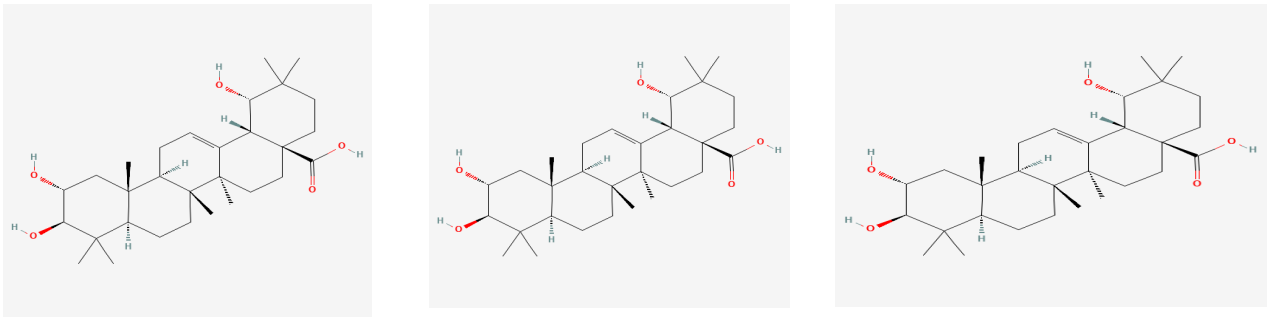
Terminalia arjuna (Roxb.) Wight & Arn. is a commonly used medicinal plant in India. It belongs to the Combretaceae family, and is popular in the Indigenous systems of medicine like Unani, Ayurveda, and Siddha, for treating cardiovascular diseases [14,15]. All parts of *T. arjuna*, including the stem bark, fruit, leaves, and roots have therapeutic qualities. The image of the plant, fruits, leaves, and stem bark of *T. arjuna* is given in figure 1.

The major constituents of *T. arjuna* in stem bark are triterpenoids- arjunolic acid, arjungenin, arjunic acid, arjunglycoside, arjunolitin, arjunoside, arjunetoside, tannnins- pentagalloyl glucose, hexadroxdiphenyl galloyl glucose, tetragalloyl glucose, ellagic acid, flavonoids- leucocyanidin, luteolin, and minerals- magnesium, calcium, zinc, and copper [19]. The chemical structure of arjunolic acid, argunjenin, and arjunic acid is given in figure 2.

T. arjuna bark extract has a long history of being used as a cardiac stimulant due to its positive effects on angina. It is also recommended for the treatment of hypercholesterolemia, heart failure, and atherosclerosis [15]. *T. arjuna*, possesses different cardioprotective properties, including positive inotropic, hypolipidemic, coronary vasodilatory, antiatherogenic, hypotensive, and antioxidant effects [19,23]. Several clinical studies have demonstrated the numerous medicinal properties of *T. arjuna.* A study by Bharani et al., 1995, revealed that adjuvant *T. arjuna* therapy in patients with refractory congestive heart failure, mostly related to idiopathic dilated cardiomyopathy, appeared safe and caused long-lasting improvement in symptoms and signs of heart failure along with improvement in left ventricular ejection phase indices with definite improvement in quality of life [24]. A study by Kapoor et al., 2015, highlighted the anti-inflammatory, anti-atherosclerotic, and immunomodulatory effects of *T. arjuna*, as an adjuvant therapy in subjects with coronary artery disease, both in in-vitro and in-vivo settings [25]. A study by Priya et al., 2019, showed

a) **b)** **c)**

Figure 1. a) Plant of Terminalia arjuna [16], b) Leaves and fruits of Terminalia arjuna [17], c) Stem bark of Terminalia arjuna [18]



a) b) c)

Figure 2. a) Chemical structure of Arjunolic acid [20], b) Chemical structure of Arjungenin [21], c) Chemical structure of Arjunic acid [22]

that *T. arjuna* bark extracts significantly reduce blood pressure and favorably modify lipid profile [26]. According to the Unani system of Medicine, *arjun* has *muraqqiq-e-dam* (blood thinner), *mufattiḥ sudad* (deobstruent), *dāfi'-i-hummā* (antipyretic), *musaffi khoon* (blood purifier), *mudirr-i-bawl* (diuretic), and *muqawwī-i-qalb* (cardiotonic) properties [27,28].
In this article, we presented the beneficial effect of *T. arjuna* on arterial stiffness in a 40-year-old male with hypertension and type 2 diabetes mellitus.

Case Report

Patient information

A 40-year-old male presented to the outpatient department of Ajmal Khan Tibbiya College and Hospital in August 2022. The patient was diagnosed with hypertension 5 years ago and type 2 diabetes mellitus 6 months ago, and was taking medicines for the same regularly. The patient was taking a combination of telmisartan (40 mg) and hydrochlorothiazide (12.5 mg) 1 tablet once daily for hypertension, and a combination of dapagliflozin (10 mg) and metformin (1000 mg) 1 tablet once daily for type 2 diabetes mellitus. The patient was healthy-looking and had a good physique. He worked as a butcher and occasionally wrestles. His younger brother had type 1 diabetes mellitus. There was no history of smoking, addiction to alcohol, or any substance abuse. There was no history of chest pain, breathlessness, palpitations, and fatigue. A signed informed consent form was obtained from the patient.

Clinical Findings

The clinical examination revealed a blood pressure of 130/80 mmHg with a pulse rate of 78 beats per minute. The patient weighed 90 kg, and his height was 166 cm. The general physical and systemic examination during interrogation were within normal limits.

Diagnostic assessment

The patient was subjected to baseline investigations, including a complete blood count (CBC), renal function test (RFT), liver function test (LFT), HbA1c (glycated hemoglobin), fasting blood sugar (FBS), and post-prandial blood sugar (PPBS), and lipid profile. All the investigations, except the lipid profile test, were within normal limits. The patient's lipid profile was deranged. The patient was screened for arterial stiffness, for which cardiovascular profile tests were performed on the patient using Diabetes Risk Profiler which showed severe arterial stiffness. Diabetes Risk Profiler, for the assessment of arterial health analysis, uses automatic simultaneous limb NiBP (non-invasive blood pressure) measurement and electrocardiogram (ECG) waveforms to calculate important parameters like central (aortic) blood pressure, arterial stiffness index (ASI), pulse wave velocities (PWV), ankle-brachial index (ABI), and ejection slope. It also includes oscillometric envelopes and interpretive nomograms. These have been established as independent markers for evaluating arterial stiffness and atherosclerosis. Atherosclerosis is evaluated by ABI, ASI, and PWV. The ASI quantifies the shape of the oscillometric envelope. It also calculates mean arterial pressure (MAP), pulse pressure, %MAP, ejection time, estimated ejection fraction, etc.

Therapeutic Intervention

The patient procured the powder of the bark of *Terminalia arjuna* (*chāl arjun*) from Elaj-e-Kamil, a retail outlet of Dawakhana Tibbiya College, Aligarh Muslim University, Aligarh. The patient was advised to take 6 g powder of *chāl arjun* and 30 mL of water (in the ratio of 1:5) and boil till the water quantity has become one-third in respect of initials. Then it was filtered through a sieve, and the decoction was consumed twice daily orally before the meal, for 12 weeks.

Follow-up

The patient was advised to follow up every 15 days. A physical examination, including BMI, and vital signs, was performed at the start of the treatment and each visit. The patient's blood glucose levels were well-controlled during the intervention. After 12

weeks of treatment, the patient was advised to repeat CBC, FBS, PPBS, HbA1c, RFT, LFT, and lipid profile and the assessment of arterial stiffness from the Diabetes Risk Profiler. Hematological and biochemical investigations at baseline and after 12 weeks of treatment are presented in table 1.

Outcome

After the completion of treatment, improvement in lipid parameters and arterial health analysis was noted. The patient's arterial health analysis improved to mild arterial stiffness. The patient tolerated the recommended medication throughout the intervention without complaints or unexpected adverse effects. The details of the arterial health analysis assessed through the Diabetes Risk Profiler are in table 2 and figure 3a-4c. The lipid profile at baseline and after 12 weeks of treatment is mentioned in table 3.

Discussion

The key strength of this case report is the significant reduction in arterial stiffness, and improvement in lipid profile with the use of *T. arjuna*. The limitation of this case report is that it cannot be used to generalize the findings of the study. Additional investigations such as high-sensitivity C-reactive protein (hs-CRP), echocardiography, computed tomography angiography, and doppler ultrasonography, were not performed.

Arterial stiffness represents a subclinical marker of cardiovascular risk and is an age-related process that is a shared outcome of many diseases including diabetes mellitus. It is an independent predictor of mortality in this population and the general population [29]. The presence of severe arterial stiffness in the patient could result from coexisting diabetes mellitus, hypertension, and increased body weight. Although arterial stiffness rises with cardiovascular aging, the process is accelerated and occurs earlier in the presence of diabetes mellitus, insulin resistance, and obesity [30]. Nuamchit et al., 2020, concluded that concomitant diabetes mellitus and hypertension significantly increase the risk of arterial stiffness, measured by cardio-ankle vascular index (CAVI) [31]. Obesity is also considered a significant risk factor for atherosclerotic vascular disease. The patient had a BMI of 32.66 kg/m^2 and was classified as obese. Arterial stiffness in obesity is emerging as an independent risk factor promoting the progression of cardiovascular disease [30]. Various previous studies have established an association between obesity and atherosclerosis. Patients with higher BMI values have more frequent and advanced atherosclerotic vascular lesions than subjects with normal body weight [32]. Despite severe arterial stiffness, the patient remained asymptomatic. Earlier studies have shown an association of diabetes mellitus with the development of subclinical and clinical cardiovascular disease [33]. The Miami Heart Study found a substantial prevalence of subclinical coronary atherosclerotic plaque in asymptomatic people [34]. Early detection and treatment of atherosclerosis are needed to reduce the burden of cardiovascular disease. After 12 weeks of treatment with the decoction of powder of *chāl arjun*, the patient showed improved lipid parameters and reduced arterial stiffness. The probable reason for improving arterial stiffness could be the antiatherogenic, hypotensive, inotropic, anti-inflammatory, anti-thrombotic, and antioxidant actions of *T. arjuna* [15]. From the perspective of Unani medicine, the possible improvement in arterial stiffness could be due to the *mufattiḥ sudad* (deobstruent), *muraqqiq-e-dam* (blood thinner), and *muqawwī-i-qalb* (cardiotonic) action of *chāl arjun*.

Various clinical studies are available proving the several medicinal properties of *T. arjuna.* Cardioprotective and cardiotonic properties in angina and poor coronary circulation, positive inotropic, anti-ischemic, antihypertensive, and antioxidant properties, have been reported by several experimental studies [19]. A review by Amalraj and Gopi, 2016, highlighted the various medicinal properties of *T. arjuna* through different studies, such as antioxidant, hypotensive, antiatherogenic, anti-inflammatory, anticarcinogenic, and antimutagenic effects [23]. Dwivedi and Agarwal, 1994, conducted a study to evaluate the effect of bark powder of *T. arjuna* in anginal frequency, blood pressure, BMI, blood sugar, cholesterol, and HDL-C in 15 stable and 5 unstable angina patients before and 3 months after *T. arjuna* therapy, and concluded that monotherapy with *T. arjuna* is fairly effective in patients with symptoms of stable angina pectoris [35]. A retrospective study by Bhawani et al., 2013, revealed that patients with dilated cardiomyopathy with reduced left ventricular ejection fraction (LVEF) due to either idiopathic or ischemic cause receiving standard therapy with *T. arjuna* showed significant improvement in left ventricular parameters, as well as functional capacity [36].

The cardioprotective effects of *T. arjuna* are partly related to its antioxidant activities, and several studies have shown that *T. arjuna* protects the heart against myocardial ischemic reperfusion injury [26]. A study by Sumitra et al., 2001 showed that arjunolic acid prevents the decrease in the levels of superoxide dismutase, catalase, glutathione peroxidase, ceruloplasmin, alpha-tocopherol, glutathione, ascorbic acid, lipid peroxide and myeloperoxidase in experimental myocardial necrosis in rats and restore the electrocardiographic changes towards normalcy. The cardioprotection of arjunolic acid pre- and post-treatment could be due to the protective effect against the damage caused by myocardial necrosis [37]. A study by

Table 1. Hematological and biochemical parameters at baseline and after 12 weeks of intervention

	At baseline	After 12 weeks
Hb (g/dL)	15.9	14.2
TLC (10^3)	7.4	8.6
RBC (10^6)	5.12	3.46
Platelet count (10^3)	189	196
ESR (mm per 1st h)	17	18
FBS (mg/dL)	127	132
PPBS (mg/dL)	154	163
S. Bil. (mg/dL) (T)	0.72	0.89
SGOT (IU/L)	37	28
SGPT (IU/L)	31	24
S. ALP (IU/L)	92	99
Blood urea (mg/dL)	36	33
S. creatinine (mg/dL)	0.96	0.94
HbA1c	5.6	5.4

Hb: Hemoglobin, TLC: Total leucocyte count, RBC: Red blood cell count, ESR: Erythrocyte sedimentation rate, FBS: Fasting blood sugar, PPBS: post-prandial blood sugar, S. Bil.: Serum bilirubin, SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamic pyruvic transaminase, S. ALP: serum alkaline phosphatase, HbA1c: Glycated hemoglobin

Table 2. Arterial health analysis at baseline and after 12 weeks of intervention

	At baseline	After 12 weeks
Arterial stiffness	Severe	Mild
Total cardiovascular risk grade	Severe	Mild
Estimated functional vascular age	54 to 56 years	48 to 50 years

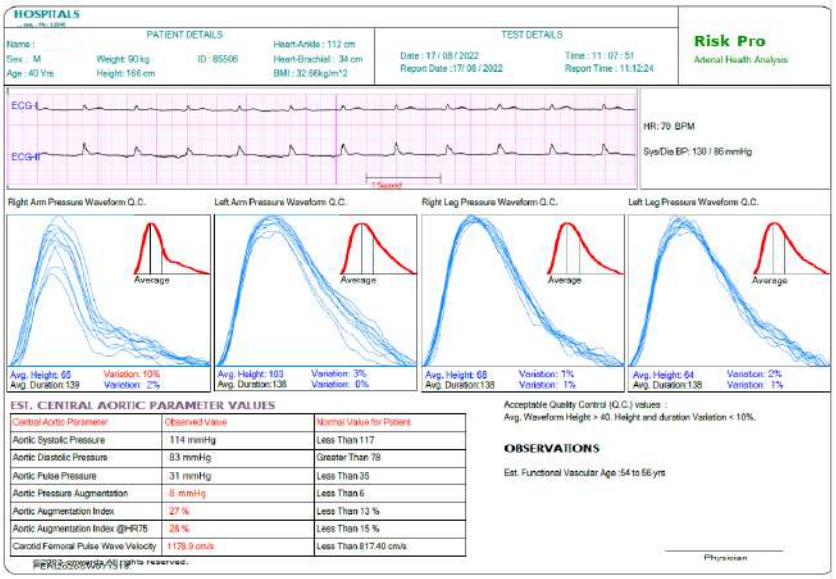
Table 3. Lipid profile at baseline and after 12 weeks of intervention

Lipid Profile	At baseline	After 12 weeks
Total serum cholesterol	214 mg/dL	196 mg/dL
Serum triglycerides	162 mg/dL	154 mg/dL
HDL-C	40 mg/dL	42 mg/dL
LDL-C	141 mg/dL	122 mg/dL
VLDL-C	32 mg/dL	30 mg/dL

HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, VLDL-C: Very low-density lipoprotein cholesterol

Manna et al., 2007 showed that the active constituents of *T. arjuna* enhanced the cardiac intracellular antioxidant activity, and histological studies also supported the protective role of *T. arjuna* [38]. Pawar and Bhutani, 2003, showed that arjungenin and its glucoside isolated from the bark of *T. arjuna* exhibited moderate free radical scavenging, and it also exhibited greater inhibitory action on the hypochlorous acid production from human neutrophils [39]. *T. arjuna* is reported to possess strong hypolipidemic properties. The saponin glycosides in *T. arjuna* are thought to be responsible for its inotropic effects; while the flavonoids/phenolics may provide antioxidant activity and vascular strengthening activity, thereby validating the various actions of this medicinal plant for its cardioprotective role [31]. A randomized control trial by Gupta et al., 2001, concluded that *T. arjuna* tree bark powder has a significant antioxidant action comparable to vitamin E and a significant hypocholesterolemic effect [40]. Subramaniam et al., 2009, conducted a study to determine the effect of the ethanolic fraction of *T. arjuna* on blood lipids and atherosclerosis in hypercholesterolemic rabbits and concluded that *T. arjuna* significantly decreases total cholesterol, LDL-C, and triglycerides levels and increases HDL-C and lessens atherosclerotic lesion in the aorta. The cardioprotective and anti-atherogenic effects of the ethanolic fraction of *T. arjuna* may be due to the presence of flavonoids, tannins, and plant sterols [41]. Based on the aforementioned studies, it can be concluded that the reduction in arterial stiffness of the patient is probably due to the effect of *T. arjuna* on serum lipoproteins

a)



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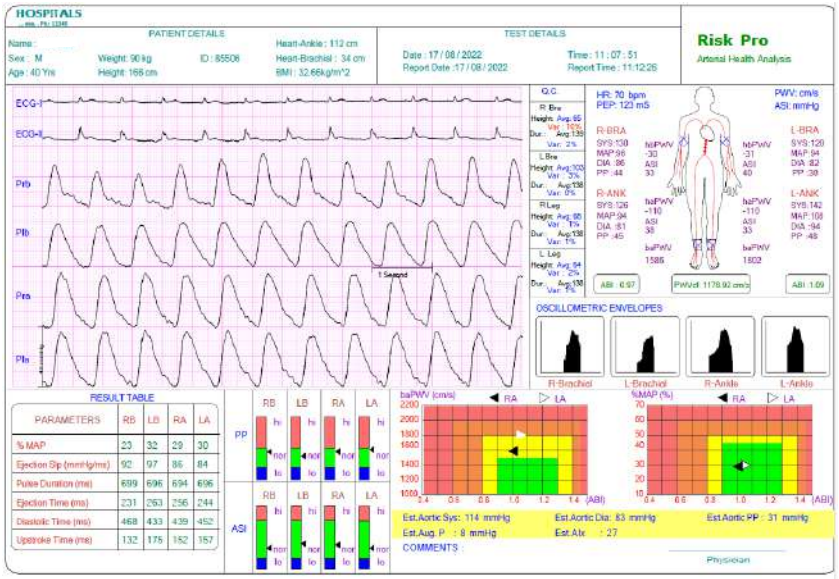

c)

Figure 3. a) Arterial health analysis from diabetes risk profiler- at baseline: estimated central aortic parameter values and estimated functional vascular age. b) Arterial health analysis from Diabetes Risk Profiler- at baseline: ABI, ejection slope, oscillometric envelopes, and carotid-femoral pulse wave velocity. c) Arterial health analysis from Diabetes Risk Profiler- at baseline: Cardiovascular risk analysis including total cardiovascular risk grade and arterial stiffness.

a)

b)

c)

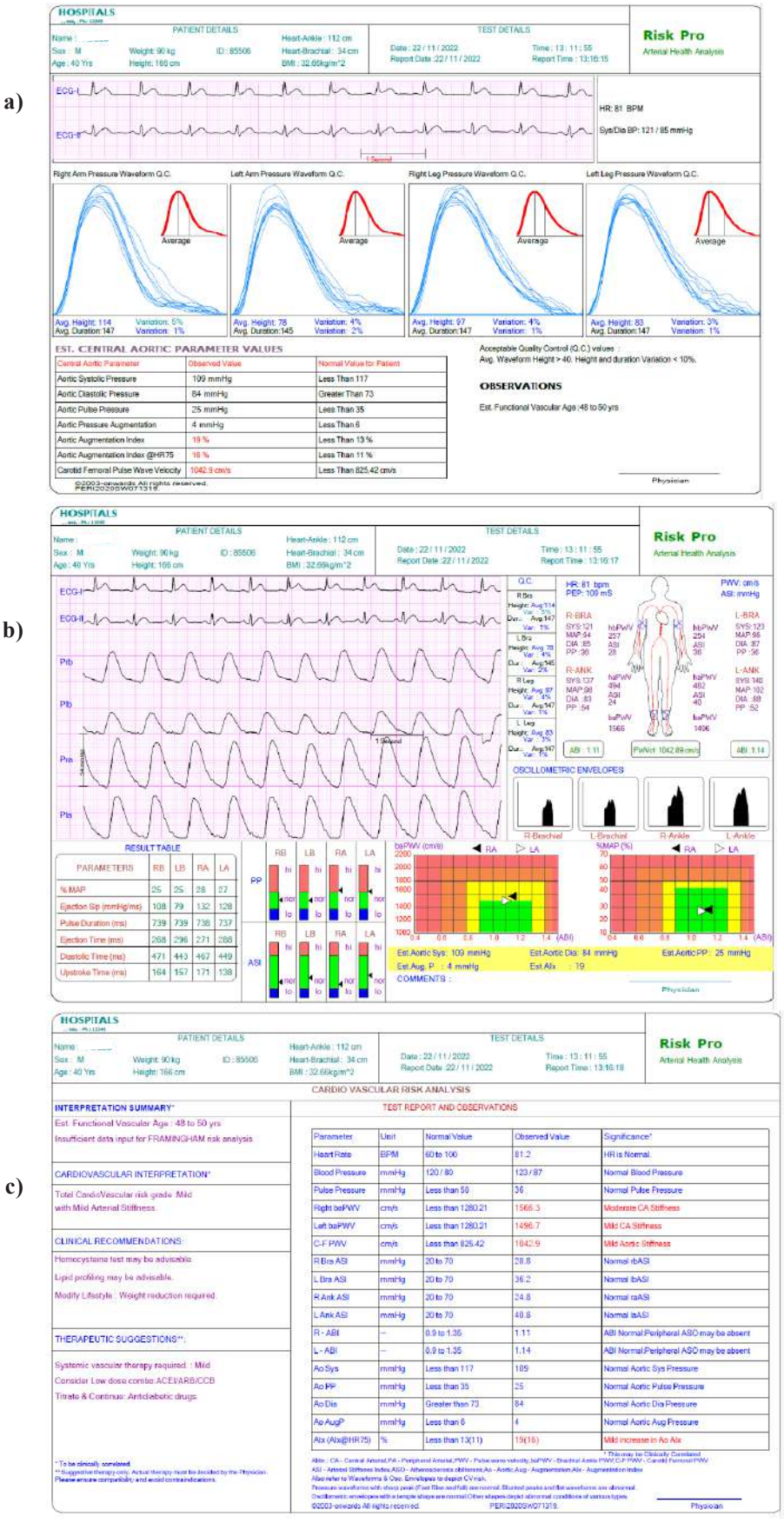

Figure 4. a) Arterial health analysis from Diabetes Risk Profiler- after 12 weeks: Estimated central aortic parameter values and estimated functional vascular age. b) Arterial health analysis from Diabetes Risk Profiler- after 12 weeks: ABI, ejection slope, oscillometric envelopes, and carotid-femoral pulse wave velocity. c) Arterial health analysis from Diabetes Risk Profiler- after 12 weeks: Cardiovascular risk analysis including total cardiovascular risk grade and arterial stiffness.

and its antioxidant and anti-inflammatory properties. In order to fully establish and demonstrate the significant potential of *T. arjuna* as a cardioprotective drug, further placebo-controlled, randomized, multi-centric clinical trials should be carried out on a larger scale to comprehensively assess the risks and benefits.

Conclusion

The results of this case report show that the powder of bark of *T. arjuna* in the form of decoction when given for 12 weeks in addition to standard medical therapy for type 2 diabetes mellitus and hypertension, in a patient with severe arterial stiffness and dyslipidemia, brought reduction in arterial stiffness, and improvement in lipid parameters. The drug exhibited favorable results without any adverse effects and was well tolerated. The findings of this case report can be used to carry out further studies with a large sample size for early detection, prevention, and reducing the progression of arterial stiffness, as well as to definitively confirm the cardioprotective effects of *T. arjuna*.

Conflicts of Interests

The authors declare that there is no conflict of interest.

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