Role of *Terminalia arjuna* Wight and Arn. in the treatment of chronic coronary artery disease from pharmacovigilance point of view

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Abstract

**Background and Objectives:** *Terminalia arjuna* Wight and Arn. (*Arjuna*) has been used in indigenous system for the treatment of cardiac ailments since 500 BC. However, there is a lack of vigilance studies during long-term therapy. The present clinical study was planned to examine the long-term safety of *Arjuna* as an adjunct drug in chronic coronary artery disease (CAD) patients. **Materials and Methods:** During the study period, a total of 35 patients of chronic CAD were enrolled to receive *Arjuna* bark extract powder (500 mg three times daily) along with conventional drugs. The control group (35 patients) received conventional drugs alone. Hemogram, liver function tests and kidney function tests were done at baseline and then every 6 months until the end of the study. Electrocardiography was done every 6 months and echocardiography was done yearly for left ventricular ejection fraction and regional wall motion abnormalities. Any adverse drug reactions reported by the patients were also recorded. **Results:** The mean age of patients in test and control groups was 60.88 ± 9.02 and 58.51 ± 12.64 years, respectively. There was a predominance of male patients in both the groups. The patients were observed for duration ranging from 9 months to 4 years and 9 months. Other than baring gastritis and constipation, no other noteworthy adverse effects were reported. No significant difference was found in laboratory value on baseline and end of therapy in both the groups. **Conclusion:** The results of the present study concluded that *Arjuna* is safe and effective in patients with chronic coronary artery disease.

**Keywords:** Adverse drug reaction, coronary artery disease, pharmacovigilance, *Terminalia arjuna*

Introduction

Most people in Southeast Asia, Africa, and some South American countries seek aid from traditional practitioners and consider herbal drugs safe and affordable. The faith on traditional medicines is deeply rooted as they have been used since generations. *Terminalia arjuna* Wight and Arn., commonly known as *Arjuna*, is one such traditional plant, belonging to the family of Combretaceae. Ancient Indian physicians used the powdered bark stem of *T. arjuna* since 500 BC for alleviating “Hritshoola” (angina) and other cardiovascular ailments.[¹] Recently, there has been renewed interest about its overall role in coronary artery disease (CAD), particularly its long-term safety in conjunction with standard antianginal treatment.

The present clinical study was planned to examine its long-term safety as an adjunct drug in patients suffering from persistent angina and/or ischemic cardiomyopathy due to chronic CAD.

Materials and Methods

This study is a prospective clinical study carried out in hemodynamically stable patients of CAD who had persistent anginal pain despite full conventional treatment during the period spanning from January 2011 to September 2015.

**Inclusion criteria**

Patients with chronic CAD with age more than 20 years were included in present study. Every patient included in this study was also having classical ECG signs of acute ischaemia, that is, presence of Q wave, ST elevation and/or T wave inversion. Supportive evidence in the form of echocardiography was also taken into account.

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also taken to assess the presence of regional wall motion abnormalities and left ventricular ejection fraction.

**Exclusion criteria**
Patients with heart failure or stroke during 3 months of the study were excluded. So also pregnant/or lactating mothers, patients with hepatic or renal failure, rheumatic valvular disease, congenital heart disease, epilepsy or those who had taken any Ayurvedic drug within past 2 weeks were also excluded from the study.

**Ethical consideration**
The study was conducted after getting approval from the Institute Human Ethics Committee (vide the approval number IEC/JH/October 2015/item 6.), and all study procedures were performed according to the Declaration of Helsinki.

**Medication**
*T. arjuna* capsule (trade name Arjuna) was purchased from Himalaya Herbal. Each capsule contained 250 mg of ethanolic extract of *Arjuna*.

During the study period (January 2011–September 2015), a total of 35 patients of chronic CAD who presented with persistent angina despite taking conventional treatment (aspirin, beta-blockers, statin, angiotensin receptor blockers, percutaneous transluminal coronary angioplasty, or bypass graft surgery) were randomly enrolled on the basis of random table over different years. They all had classical ECG signs of acute ischemia, that is, the presence of Q wave, ST elevation and/or T wave inversion. Supportive evidence in the form of echocardiography was also taken to assess the presence of regional wall motion abnormalities and LVEF. They were then administered bark extract (ethanolic extract) powder capsule (500 mg three times daily) along with conventional drugs after informed consent. Lifestyle measures, particularly no oral tobacco consumption or smoking habits, were strictly enforced.

The control group included 35 patients enrolled during the same period who received conventional drugs comprising aspirin 75 mg/day, metoprolol XI 50 mg/day, statin 20 mg/day, nitrocontin 2.6 mg/day and antihypertensive angiotensin receptor blocker telmisartan 20–40 mg/day as per requirement and oral antidiabetic drugs as per their blood sugar level.

**Measurements and assessment**
Patients were asked to maintain an angina diary, sense of well-being, and/or any untoward symptoms. They were followed up every 6 months. All the blood investigations were done at baseline and then every 6 months till the end of the study. The investigations carried out were hematological tests (hemoglobin and total leukocyte count); S. triglyceride, liver function tests that included serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), total bilirubin and alkaline phosphatase (ALP); and kidney function tests such as blood urea and serum creatinine. ECG was done every 6 months, and echocardiographic assessment was done yearly for LVEF and regional wall motion abnormalities.

**Outcomes**
The primary endpoint of the study was percentage change from baseline in measured levels of hematological and biochemical parameters like triglycerides at the end of treatment. In addition to this, any other suspected adverse drug reactions (ADRs) reported by the patients were also recorded.

The secondary endpoints for this study included persistence of chest pain for >3 times in a day, new chest pain >5 min, appearance of congestive heart failure, necessity to get admitted in coronary care unit, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting or sudden cardiac death.

**Statistical analysis**
Statistical analysis was done using SPSS version 20 (SPSS Software Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA). The data generated are presented as mean (standard deviation). The normality of data was tested by the Shapiro–Wilk test. For parametric data, “paired t-test” tested the level of significance between the baseline and the end of study period in the groups. *P* < 0.05 was considered as statistically significant.

**Results**
The total number of patients enrolled (in either group) in 2011, 2012, 2013, 2014 and 2015 were 7, 7, 13, 4, and 4 respectively. There were no dropouts. The mean age of the patients in the test and control groups was 60.88 ± 9.02 and 58.51 ± 12.64 years, respectively. The male-to-female ratio in the test group was 23:12 and in the control group was 19:16.

Other characteristics of the patients in the test and control groups are given in Table 1. Although the frequency of anginal pain and echocardiographic LVEF improvement was observed in both the groups, patients taking *Arjuna* bark extract were noted to have better feeling of wellness and lesser intensity of chest pain. None of the patients who were on *Arjuna* needed hospitalization, angioplasty and/or bypass graft surgery.

Mild adverse effects were seen pertaining to the gastrointestinal system: gastritis (two patients) and constipation (one patient). No other untoward effects were reported by the patients in the *Arjuna* group. There was no mortality in both the groups. In the control group, two cases needed angioplasty and one required bypass surgery.

**Table 1: Characteristics of patients in the two groups**

| Patients’ characteristics | Test group (n=35) | Control group (n=35) |
|--------------------------|------------------|---------------------|
| Smoking/tobacco chewing  | 6 (17.14)        | 5 (14.28)           |
| Diabetes                 | 9 (25.71)        | 10 (28.57)          |
| Hypertension             | 18 (51.43)       | 20 (57.14)          |
| Hyperlipidemia           | 3 (8.57)         | 1 (2.86)            |
| CAD alone                | 5 (14.28)        | 4 (11.43)           |

Within-bracket values depict the percentage in each category. CAD: Coronary artery disease
The baseline and end of study values (for both the groups) for hemoglobin, total leukocyte count, bilirubin, SGOT, SGPT, ALP, blood urea and serum creatinine have been shown in Tables 2 and 3. No significant difference was observed in the baseline and end of therapy laboratory values in the treatment and control groups.

**Discussion**

Safety and efficacy are recognized as equally requisite attributes as a therapeutic attribute of any medicine. Pharmacovigilance methods were initially developed for monitoring pharmaceutical medicines and to detect drug adverse events that have previously been unrecognized despite evaluation in clinical trials. It is believed that herbal drugs are free from any adverse effects, but it is not always true. As a matter of fact, herbal medicines are chemically rich and complex products and as pharmaceutical drugs not isolated single compounds. Nevertheless, unexpected adverse events of herbal products can occur, including fatal episodes which may arise from the misuse of the wrong species of medicinal plants, incorrect dose, incorrect processing methods, interactions with concomitant medicines, adulterated/contaminated herbs, contamination with toxic metals, or pathogenic microorganisms.

Thus, pharmacovigilance has paramount importance in detecting unwanted reactions in relation to herbal medicine. Many of the herbal products in the market have not been thoroughly tested for their pharmacology and toxicology. Hence, pharmacovigilance has an essential role in developing reliable information on the safety of herbal medicines. Recognizing this, WHO has developed guidelines for the monitoring of herbal safety.

Further many herbal products sold in the market have not been thoroughly tested for their toxicity. Thus, making the notion these being safe is treacherously deceptive. Evidence from the literature has revealed the fact that consumers tend to self-prescribe herbal medicines without consulting a health professional. These products can be bought over-the-counter from pharmacies without any prescription and this practice can be dangerous.

**Arjuna** has been in use for long and is considered to be effective for angina with no major side effects in short-term studies. However, pharmacovigilance studies during long-term therapy have not been conducted so far. To the best of our knowledge, this is the first-ever clinical report, examining long-term effects of T. arjuna on hematological, renal and liver functions. Notably, it conferred a better sense of well-being and lesser intensity of chest discomfort in patients taking this in addition to conventional drugs. In fact, one of our patients was taking **Arjuna** decoction for his hypertension for the past 15 years on the basis of folklore belief but was never subjected to any hematological, renal, or liver profile checkup. When the patient was investigated fortunately, the drug did not show any adverse effects on any of the laboratory parameters. In addition to the present study, Kumar *et al.* study showed that there were no significant changes in serum alanine aminotransferase, aspartate transaminase, ALP and bilirubin, urea and creatinine at the end of study as compared to baseline levels in patients of dyslipidemia receiving **Arjuna** powder for 3 weeks, followed by **Arogyavardhini Vati** for 4 weeks.

Suganthi *et al.* assessed the safety of the methanolic extract of **Arjuna** in acute, subacute, and *in vitro* toxicity studies. They found no significant alteration in hematological, biochemical and morphological parameters and the *in vitro* test revealed that **Terminalia chebula, T. arjuna** and 7-methyl gallic acid are devoid of cytotoxicity, mutagenicity and genotoxicity up to optimum dosage.

Further, herbal medicines have been reported to contain pharmacologically active ingredients, some of which have been associated with adverse events. A systematic review by Podazaski has shown that adverse events can range from mild to severe. Mild adverse events included pain, allergic reactions, dermatitis, dizziness, dry mouth, fatigue,

### Table 2: Hematological parameters of patients

| Parameters                        | Groups                      | 2011 (n=7) | 2012 (n=7) | 2013 (n=13) | 2014 (n=4) | 2015 (n=4) |
|----------------------------------|-----------------------------|------------|------------|-------------|------------|------------|
| Hemoglobin (12-16 g/dl)          | Baseline                    |            |            |             |            |            |
|                                  | Control                     | 13.4±2.5   | 13.7±2.5   | 14.02±1.5   | 13.8±1.9   | 13.8±1.8   |
|                                  | Test                        | 13.7±1.5   | 14.4±1.6   | 13.5±1.7    | 13.2±1.1   | 12.5±1.7   |
|                                  | End of therapy              | 13.0±2.4   | 13.6±2.4   | 13.6±1.5    | 13.92±1.7  | 13.4±1.6   |
|                                  | Control                     | 13.4±1.3   | 14.0±1.8   | 13.6±1.5    | 13.6±1.9   | 12.4±1.2   |
|                                  | Test                        |            |            |             |            |            |
| Total leukocyte count (4000-11,000 cells/µl) | Baseline                    | 7142.9±1022.8 | 6182.9±1.9  | 7014.6±1682.9 | 6420±2396.7 | 6462.5±980.9 |
|                                  | Control                     | 7042.9±1991.5 | 8800±1300  | 7254.5±1448.7 | 7425±903.2 | 7100±1820.2 |
|                                  | Test                        | 6950±1170.1 | 6314.3±1.9 | 7065.4±1679.9 | 6610±2527.8 | 6737.5±919.6 |
|                                  | End of therapy              | 7057.1±1919.9 | 8771.4±1866.1 | 7418.2±1533.5 | 7525±1081.3 | 7000±1984.9 |

All the values are mean±SD. Here, “end of therapy” refers to September 2015 for both the groups. There was no significant difference in the parameters at baseline and end of therapy in both the groups (P>0.05). SD: Standard deviation.
gastrointestinal upset, and muscle weakness. Moderately severe adverse events included anorexia, reversible neutropenia, coagulation abnormalities, confusion, slurred speech, blurred vision, sedation, electroencephalogram changes, loss of consciousness, vertigo and photophobia. Severe adverse events could be acute psychosis, cerebral hemorrhage, coma, respiratory arrest, tachycardia, renal failure and death. In addition, herbal medicines have been reported to cause chest discomfort, ventricular arrhythmias and also snowballing chronic or delayed toxicity. Aristolochic acid nephropathy is a very good example of chronic toxicity. The effects are cumulative and renal symptoms can be delayed for 2 years after stopping the use of the herbs. The pattern of toxicity can only be recognized in cluster of cases in Belgium with detailed follow-up. This suggests that if the first signs of adverse effects are not recognized until months or years after starting or even stopping the use of the herbal medicine, the use of the herbs is likely to be forgotten with such a delay. This calls for an alert that herbal medicine cannot be always safe.

Besides its potential adverse effect on long-term use, its interaction with other cardiovascular drugs such as aspirin, statin, beta-blocker, and angiotensin-converting enzyme (ACE)-inhibitor group of drugs also needs to be considered. A study by Asad et al. based on parameters, such as caking, liquefaction, odor, color and gel formation, found no change in the physical properties of *T. arjuna* alone and mixture of

### Table 3: Biochemical parameters of patients

| Parameters                  | Groups     | Year of enrollment | 2011 (n=7) | 2012 (n=7) | 2013 (n=13) | 2014 (n=4) | 2015 (n=4) |
|-----------------------------|------------|--------------------|------------|------------|------------|------------|------------|
| **Serum bilirubin (0.3-1.9 mg/dl)** | Baseline  | 2011 (n=7)        | 0.8±0.2    | 0.5±0.3    | 0.6±0.2    | 0.7±0.2    | 0.6±0.2    |
|                             | Control    | 2012 (n=7)        | 0.5±0.3    | 0.7±0.4    | 0.4±0.2    | 0.6±0.1    | 0.6±0.2    |
|                             | Test       | 2011 (n=7)        | 0.7±0.2    | 0.4±0.2    | 0.6±0.2    | 0.6±0.2    | 0.6±0.2    |
|                             | Control    | 2012 (n=7)        | 0.3±0.2    | 0.4±0.2    | 0.5±0.2    | 0.5±0.2    | 0.4±0.2    |
|                             | Test       | 2011 (n=7)        | 0.3±0.2    | 0.4±0.2    | 0.5±0.2    | 0.5±0.2    | 0.4±0.2    |
| **SGOT (5-40 U/L)**         | Baseline  | 2011 (n=7)        | 32.6±14.4  | 31.7±10.6  | 29.5±11.7  | 26.8±2.8  | 29.3±7.4  |
|                             | Control    | 2012 (n=7)        | 23.7±6.7   | 28.4±6.9   | 26.4±9.4   | 28.9±6.4  | 33.3±12.3 |
|                             | Test       | 2011 (n=7)        | 33.1±9.8   | 30.4±8.2   | 28.2±10.7  | 25.3±3.1  | 27.3±5.6  |
|                             | Control    | 2012 (n=7)        | 19.6±3.5   | 24.7±4.7   | 24.2±7.4   | 22.5±3.8  | 32.3±7.1  |
|                             | Test       | 2011 (n=7)        | 19.6±3.5   | 24.7±4.7   | 24.2±7.4   | 22.5±3.8  | 32.3±7.1  |
| **SGPT (7-56 U/L)**         | Baseline  | 2011 (n=7)        | 38.9±16.7  | 31.1±10.2  | 34.8±15.9  | 32±7.5    | 32±14.6   |
|                             | Control    | 2012 (n=7)        | 27.9±10.9  | 36.3±14.7  | 31.4±9.9   | 37.9±18.2 | 41.8±28.3 |
|                             | Test       | 2011 (n=7)        | 37.6±12.9  | 29.1±9.1   | 37.3±17.6  | 29.5±13.7 | 29.9±12.1 |
|                             | Control    | 2012 (n=7)        | 23±6.8     | 31±11.3    | 29.2±7.8   | 37±13.4   | 32.8±19.3 |
|                             | Test       | 2011 (n=7)        | 23±6.8     | 31±11.3    | 29.2±7.8   | 37±13.4   | 32.8±19.3 |
| **ALP (20-140 IU/L)**       | Baseline  | 2011 (n=7)        | 86.4±20.1  | 90.6±19.4  | 77.6±23.3  | 88±15.8   | 104.2±13.7 |
|                             | Control    | 2012 (n=7)        | 90.1±16.6  | 85±24.5    | 75.3±25.9  | 97.5±18   | 90.3±27.5 |
|                             | Test       | 2011 (n=7)        | 87.1±26.8  | 88.9±19.7  | 75.2±22.4  | 85.8±23.5 | 110.8±20.6 |
|                             | Control    | 2012 (n=7)        | 82.6±26.1  | 72.6±21.8  | 69±5.6     | 88±24.9   | 61.5±32.2 |
|                             | Test       | 2011 (n=7)        | 82.6±26.1  | 72.6±21.8  | 69±5.6     | 88±24.9   | 61.5±32.2 |
| **Blood urea (15-58 mg/dl)**| Baseline  | 2011 (n=7)        | 23.9±7.4   | 23.7±3.9   | 29±7.9     | 22.8±7.3  | 27±7.3    |
|                             | Control    | 2012 (n=7)        | 27.7±6.2   | 28.4±8.4   | 28.3±7.1   | 30.3±2.6  | 25.5±4.3  |
|                             | Test       | 2011 (n=7)        | 24.1±7.3   | 25.1±3.4   | 28±7.2     | 23.8±10.3 | 27±7.3    |
|                             | Control    | 2012 (n=7)        | 26.7±8.2   | 24.2±7.6   | 25.6±4.6   | 30.8±5.4  | 24±3.6    |
|                             | Test       | 2011 (n=7)        | 26.7±8.2   | 24.2±7.6   | 25.6±4.6   | 30.8±5.4  | 24±3.6    |
| **Serum creatinine (0.7-1.5 mg/dl)** | Baseline  | 2011 (n=7)        | 0.8±0.3    | 0.7±0.2    | 0.9±0.2    | 0.8±0.3   | 0.8±0.2   |
|                             | Control    | 2012 (n=7)        | 0.9±0.3    | 1.1±0.3    | 0.9±0.3    | 1.2±0.2   | 0.9±0.2   |
|                             | Test       | 2011 (n=7)        | 0.7±0.3    | 0.8±0.2    | 0.8±0.4    | 0.8±0.2   | 0.9±0.2   |
|                             | Control    | 2012 (n=7)        | 0.9±0.3    | 0.9±0.4    | 0.9±0.3    | 1.0±0.3   | 0.8±0.2   |

All values are mean±SD. Here, “end of therapy” refers to September 2015 for both the groups. There was no significant difference in the parameters at baseline and end of therapy in both the groups (P>0.05). SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, ALP: Alkaline phosphatase, SD: Standard deviation.
T. arjuna and the common cardiovascular drugs. The study also revealed that there is no interaction of T. arjuna with other cardiovascular drugs. T. arjuna can, therefore, be used safely along with these drugs.\[16\]

**Conclusion**

The present study shows that the administration of T. arjuna along with conventional drugs such as aspirin, beta-blocker, ACE inhibitor and statins does not show any adverse effects on hematological, renal or hepatic parameters even after 4–5 years.

The use of T. arjuna has increased under the belief that this is effective and safe. There was a lack of information on the safety of this drug. This called for an able pharmacovigilance study team to build up unswerving information on the safety of T. arjuna, similar to that of the conventional modern drugs. It is essential to identify adverse events in patients taking herbal drugs so that appropriate warnings and guidelines can be given to practitioners and patients. There was a lack of information on the safety of herbs, which calls for an effectual pharmacovigilance program for the development of appropriate recommendations for safe and effective use.

**Strength of the study**

This is the first-ever study on the long-term safety of T. arjuna and its effect on the sense of well-being in CAD patients.

**Limitations of the study**

The number of study participants is quite small, particularly in later years. Herbal formulations are usually not standardized and so there may be differences in toxicity between preparations.

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**Conflicts of interest**

There are no conflicts of interest.

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