Annals of Phytomedicine 5(2): 45-49, 2016
Journal homepage: www.ukaazpublications.com
Print ISSN : 2278-9839 and Online ISSN : 2393-9885

ANNALS OF PHYTOMEDICINE
An International Journal

Case study

Compatibility of *Terminalia arjuna* (Roxb.) Wight & Arn. with common cardiovascular drugs

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Received September 20, 2016: Revised October 10, 2016: Accepted October 15, 2016: Published online December 30, 2016

Abstract

Terminalia arjuna (Roxb.) Wight & Arn. is a herbal medicinal plant that is used in treatment of a large number of diseases, especially cardiac diseases along with common cardiovascular drugs like metoprolol, atorvastatin, enalapril maleate and aspirin. The aim of present study was to find out the safety of *T. arjuna* when co-administered with these drugs. Commercially available *T. arjuna* (Himalaya Herbal) was used for this studies. *T. arjuna* contains a number of active compounds that may have drug interaction. Based on parameters such as caking, liquefaction, odor, color and gel formation, no change was seen in the physical properties of *T. arjuna* alone and mixture of *T. arjuna* and cardiovascular drugs. The comparison of λ_{max} values of individual drugs and their mixture with *T. arjuna* revealed that there is no interaction of *T. arjuna* with these cardiovascular drugs. *T. arjuna* can therefore be used safely along with these drugs.

Keywords: *Terminalia arjuna*, drug interaction, cardiovascular drugs

1. Introduction

The demand of herbal medicines is increasing continuously due to their effectiveness, low side effect and relatively low cost (Iqbal, 2013; Pushpangadan, 2013; Subramonian, 2014; Oga *et al*., 2016). Use of herbal medicines as self prescribed drugs has increased from 2.5% to 12% and their prescription by medical practitioner has also increased from 10.2% to 15.1% (Miller, 1998; Bressler, 2005). According to WHO report 11,000 plants are used medicinally in which 500 herbs and plants are used in complementary medicines (Bruce, 2008). The popularity of herbal drugs requires an understanding of their interaction with prescribed drugs (Valli and Giardina, 2002; Udupa, 2016). The herb-drug interaction may be greater than drug-drug interaction because herbal drugs contain a number of active compounds while allopathic drugs mostly have a single compound (Berman and Ernst, 2001). However, herbal drugs are capable of affecting the pharmacodynamics and pharmacokinetics of co-administered allopathic drugs. Simultaneous administration of herbal drugs with allopathic drugs can magnify, mimic or oppose the effect of allopathic drugs (Berman, 2000; Evans and Mcleod, 2003; Oga *et al*., 2016). A number of reports have appeared in literature citing adverse effects of drug interactions. Some of the common adverse effects are enhanced anticoagulation leading to increase in time of blood clotting, hypoglycemia, hyperlipidemia, increased or decreased blood pressure, venous insufficiency, hypertension, intermittent claudication, congestive heart failure, gastrointestinal toxicity, coma, serotonin syndrome, allergic reaction, etching and many more. However, these effects depend on herbal medicine, allopathic drugs and patients also (Ernst, 1998; Cupp, 1999; Valli and Giardina, 2002; Hu *et al*., 2005). The present study was carried out with the aim to determine any physical and chemical interaction of *Terminalia arjuna* with cardiovascular drugs and to find out the safety of its use in conjunction with cardiovascular drugs like aspirin, metoprolol, atorvastatin and enalapril maleate.

Terminalia arjuna belongs to Combretaceae family and is distributed in India, Sri Lanka and Burma. In India the bark of *T arjuna* is used as a herbal drug for treatment of large number of diseases from ancient times. Tannins and polyphenols present in *T. arjuna* show anticancer property, while triterpenoids act as cardiotonic (Jain and Yadav, 2009). In India many of the patients of cardiac disease such as coronary artery disease, heart failure, hypercholesterolemia and angina pain are prescribed *T. arjuna* along with allopathic drugs like aspirin, enalapril maleate, metoprolol and atorvastatin (Dwivedi and Jauhari, 1997; Kandil and Nassar, 1998; Dwivedi, 2007; Kumar, 2014). The herbal drug has been used traditionally for long time and has been mentioned since Vedic period in several ancient Indian medicinal texts including Charaka Samhita, Sushruta Samhita, and Astang Hridayam. It also has good aesthetic value and is considered as safe drug. (Dwivedi, 2007; Kumar, 2014). Due to the perception of its safety, people use this medicine regularly in various dosage forms with other cardiovascular medicine. Any drug–drug interaction may cause serious implication or toxicity.

2. Materials and Methods

2.1 Materials

T. Arjuna capsule (trade name Arjuna) was purchased from Himalaya Herbal, Aspirin tablet 75 mg from Taj Pharmaceuticals, Metoprolol tablet (Betaloc) 50 mg from Astrazeneca Pharma India Ltd, Atorvastatin tablet (Atorva) 40 mg from Zydus Cadila and Enalapril maleate tablet (Envas) 5 mg from Cadila Pharmaceuticals.

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DOI: 10.21276/ap.2016.5.2.5

2.2 Methods

2.2.1 *Physical examination*

Physical examination of the drug was done by modifying the protocol of Parveen *et al*. (2015). The drugs alone and a homogenous mixture of Arjuna and Aspirin, Arjuna and Metoprolol, Arjuna and Atorvastatin, Arjuna and Enalapril were prepared in a ratio of 1:1 using mortar pestle. Each mixture (powder form) was divided into 3 groups (200 mg each), which was kept in three different conditions, 25ºC, 40ºC and 50ºC in hot air oven (Vinod Scientific Works). The selection of temperature was based on previous reports from this laboratory for similar studies (Parveen *et al*., 2015). Physical properties such as odor, color, caking, liquefaction and gel formation were visually observed.

2.2.2 *Qualitative analysis*

Serial dilution of drugs was made (1000 µg/ml, 500 µg/ml, 250 µg/ml, 125 µg/ml, 62.5 µg/ml, 31.25 µg/ml and 15.625 µg/ml) and 62.5 µg/ml as well as 100 µg/ml of Arjuna, aspirin, Arjuna+aspirin, metoprolol, Arjuna+metoprolol, atorvastatin, Arjuna+atorvastatin, enalapril maleate, Arjuna+enalapril maleate dissolved in water, dilute HCl (pH 2.5), dilute NaOH (pH 8.0) and methanol respectively, were scanned on Perkin elmer lambda Bio 20 spectrometer at wavelength range of 200-700 nm for getting λ_{max} of Arjuna, aspirin, metoprolol, atorvastatin, enalapril and mixture of Arjuna+aspirin, Arjuna+metoprolol, Arjuna+atorvastatin, Arjuna+enalapril (Bonazzi *et al*., 1997; Sirajuddin *et al*., 2013).

3. Results

3.1 Physical examination

T. arjuna, the common cardiovascular drugs and the mixture of these drugs with *T. arjuna* were kept at 25ºC, 40ºC and 50ºC for three weeks and following properties were observed by smell and visualization. The single drugs as well as their mixtures showed no caking and no clump formation was observed. It showed no change in solid state and there was no liquefaction. Odor was same, no gel formation or change in color was seen in any of the mixtures (Table 1).

Table 1: Physical examination of Arjuna, Aspirin, Metoprolol, Enalapril and mixture of Arjuna and above tested drugs

Temperature (ºC)	Sample	Caking	Liquefaction	Odor change	Gel formation	Color change
25ºC	Arjuna	no	no	no	no	no
	Aspirin	no	no	no	no	no
	Metoprolol	no	no	no	no	no
	Atorvastatin	no	no	no	no	no
	Enalapril	no	no	no	no	no
	Arjuna+Aspirin	no	no	no	no	no
	Arjuna+Metoprolol	no	no	no	no	no
	Arjuna+Atorvastatin	no	no	no	no	no
	Arjuna+Enalapril	no	no	no	no	no
40ºC	Arjuna	no	no	no	no	no
	Aspirin	no	no	no	no	no
	Metoprolol	no	no	no	no	no
	Atorvastatin	no	no	no	no	no
	Enalapril	no	no	no	no	no
	Arjuna+Aspirin	no	no	no	no	no
	Arjuna+Metoprolol	no	no	no	no	no
	Arjuna+Atorvastatin	no	no	no	no	no
	Arjuna+Enalapril	no	no	no	no	no
50ºC	Arjuna	no	no	no	no	no
	Aspirin	no	no	no	no	no
	Metoprolol	no	no	no	no	no
	Atorvastatin	no	no	no	no	no
	Enalapril	no	no	no	no	no
	Arjuna+Aspirin	no	no	no	no	no
	Arjuna+Metoprolol	no	no	no	no	no
	Arjuna+Atorvastatin	no	no	no	no	no
	Arjuna+Enalapril	no	no	no	no	no

3.2 Qualitative analysis

After preliminary observation with serial dilution of *T. arjuna*, cardiovascular drugs and mixture of drugs, (62.5 µg/ml and 100 µg/ml), dissolved in water, dilute HCl (pH 2.5), dilute NaOH (pH 8.0) and methanol, respectively, were selected for further study. The λ_{max} of Arjuna was 277 nm, aspirin 296 nm while mixture of Arjuna and aspirin shows 279 nm (Table 2). There is no significant difference in λ_{max} of Arjuna and aspirin mixture. The λ_{max} of metoprolol was 274 nm the mixture of Arjuna and metoprolol showed 275 nm. Atorvastatin alone showed the λ_{max} of 241 nm and the mixture of Arjuna and atorvastatin shows 275 nm. As the λ_{max} of Arjuna is 277 nm, there is no significant difference when two drugs are mixed. Enalapril showed the λ_{max} 279 nm and mixture of Arjuna and enalapril also showed 279 nm. Again, there is no difference in λ_{max} of mixture and enalapril.

The difference of λ_{max} in Arjuna and mixture of Arjuna and aspirin was 2 nm, metoprolol and mixture of Arjuna and metoprolol was 1 nm, atorvastatin and mixture of Arjuna and atorvastatin was 2 nm, but there was no change in λ_{max} of enalapril and mixture of Arjuna and enalapril. The difference between the λ_{max} value of *T. arjuna* alone and in mixture with the tested drugs was not significant. This reflects that cardiovascular drugs do not interact with *T. Arjuna* and do not affect its stability when present in mixture form. The degradation of drugs alone or in mixture with Arjuna upon storage at different temperatures for three weeks was same.

Table 2: Table showing the λ_{max} of Arjuna, Aspirin, Metoprolol, Atorvatatin, Enalaril and mixture of Arjuna and above tested drugs.

Sample	Water (62.5 µg/ml)	Water (100 µg/ml)	Diluted HCl (pH-2.5)	Diluted NaOH (pH-8.0)	Methanol
Arjuna	277 nm	277 nm	277 nm	277 nm	277 nm
Aspirin	296 nm	296 nm	296 nm	296 nm	296 nm
Arjuna+Aspirin	279 nm	279 nm	279 nm	279 nm	279 nm
Metoprolol	274 nm	274 nm	274 nm	274 nm	276 nm
Arjuna+ Metoprolol	275 nm	275 nm	275 nm	275 nm	276 nm
Atorvastatin	241 nm	241 nm	241 nm	242 nm	241 nm
Arjuna+Atorvastatin	275 nm	275 nm	275 nm	275 nm	274 nm
Enalapril	279 nm	279 nm	279 nm	279 nm	279 nm
Arjuna+Enalapril	279 nm	279 nm	279 nm	279 nm	279 nm

4. Discussion

T. arjuna is often used as home remedy and is also prescribed along with other drugs for cardiac diseases as an Ayurvedic medicine or dietary supplement. The bark extract of *T. arjuna* has likewise indicated defensive impacts against doxorubicin-prompted DNA damage and cardiotoxicity (Singh *et al*., 2008). *T. arjuna* protects the heart against myocardial changes affected by perpetual β-adrenoceptor incitement (Maulik and Talwar, 2012). The drug has been used traditionally since ancient times and is mentioned in Vedic literature; it also has good aesthetic value as well as considered as safe drug (Kumar, 2014). Due to the perception of its safety peoples use this medicine in various dosage forms with other cardiac medicines.

Aspirin have been reported to have interaction with ginkgo and can cause severe spontaneous bleeding (Izzo and Ernst, 2001). Phenelzine with ginseng causes irritability and hallucinations, *Hypericum perforatum*, a flowering plant commonly known as St John's wort, is prescribed during heart transplant, kidney transplant, liver transplant, lung fibrosis, depression, migraine, type I diabetes, asthma, polymorbid and many other diseases. It shows interaction with cyclosporine, loperamide, oral contraceptives, nefadozone, sertraline, peroxitine, theophylline, phenprocoumon, and warfarin cause many side effects like lowering of blood and plasma cyclosporine level, changed menstrual bleeding, disoriented, agitated and confused state, inter-menstrual bleeding, nausea, vomiting, headache, dizziness, weakness, decreased INR, *etc*. (Izzo *et al*., 2005). By keeping these interactions in mind, the study was planned to assess the interaction, if any, of Arjuna with these cardiovascular drugs.

The Arjuna powder was mixed separately with aspirin, enalapril, atorvastatin and metoprolol in equal quantity and kept for 21 days at 25°C, 40°C and 50°C with reference to single drug powder observe the physicochemical changes. After every week samples were observed for caking, liquefaction, odor, gel formation and color changes. The samples were also withdrawn from every lot for UV Spectrophotometric analysis at the end of 3rd week. No physical change was observed in parameters such as caking, liquefaction, odor, color change and gel formation in samples on storing up to 3 weeks under various conditions.

The result of UV Spectrophotometric analysis (Figure 1 a,b,c,d) showed similar pattern of λ_{max} after 3 weeks with reference to the samples at zero time; the shift in λ_{max} upon mixing of Arjuna with drugs is not significant. These results suggest that there is no interaction of *T. arjuna* with aspirin, metoprolol, atorvastatin, and enalapril. *T. arjuna* may, therefore, be used safely with these common cardiovascular drugs.

5. Conclusion

Previously it is reported that aspirin shows the interaction with gingko, however, our finding show that there is no interaction of aspirin with Arjuna. Preliminary evaluation concluded that Arjuna is not having any physico-chemical interaction with the tested cardiovascular drugs. Physical examination showed similar properties such as color, odor as well as no liquefaction. Qualitative analysis showed similar pattern of λ_{max} that indicate there is no interaction of Arjuna with these cardiovascular drugs. Thus *T. arjuna* can be used safely in combination with the cardiovascular drugs.

Acknowledgements

Authors are thankful to Jamia Hamdard (Hamdard University) for providing necessary facilities to carry out this study.

Conflict of interest

We declare that we have no conflict of interest.

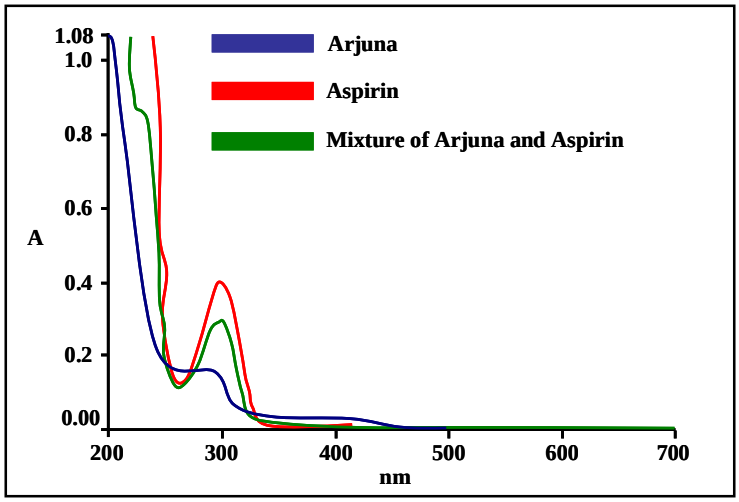

Figure 1(a): UV-VIS scan of Arjuna, Aspirin and mixture of Arjuna and Aspirin in water (100 µg/ml)

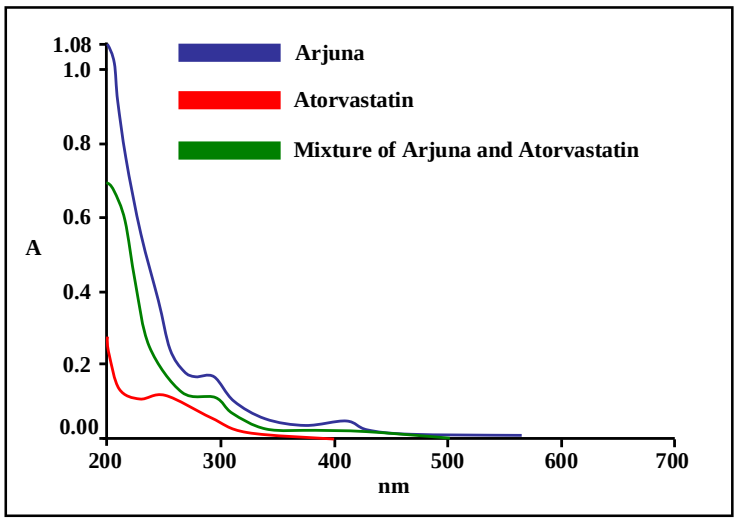

Figure 1(b): UV-VIS scan of Arjuna, Atorvastatin and mixture of Arjuna and Atorvastatin in water (100 µg/ml)

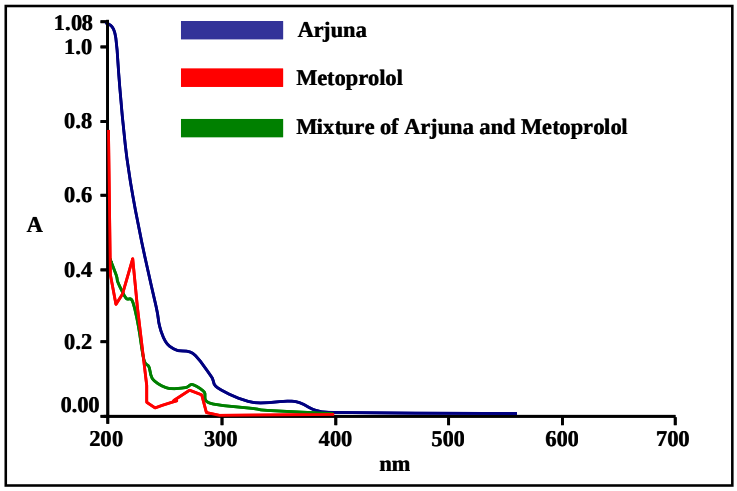

Figure 1(c): UV-VIS scan of Arjuna, Metoprolol and mixture of Arjuna and Metoprolol in water (100 µg/ml)

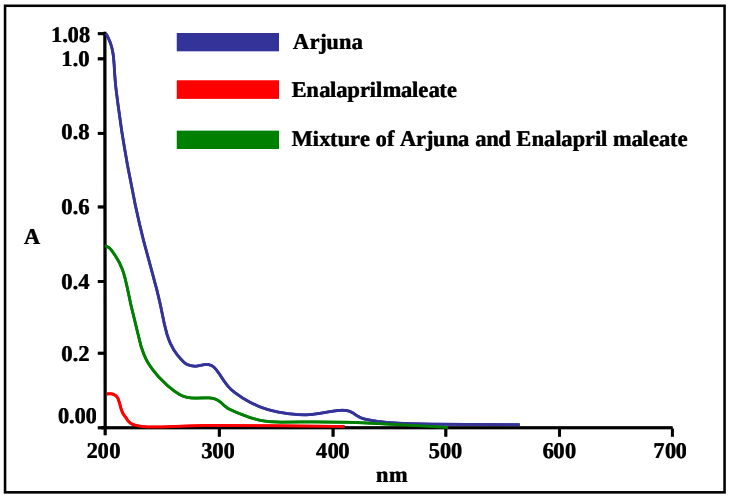

Figure 1(d): UV-VIS scan of Arjuna, Enalapril maleate and mixture of Arjuna and Enalapril maleate in water (100 µg/ml)

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