Review Article

Terminalia arjuna: Alternative Treatment for Cardiovascular Diseases

Isha Zafar, R.K. Sharma, Shama Mujawar[*], Sameer Choudhary
Jyoti Vidyapeeth Women's University, Jaipur and RASA Life Science Informatics, Pune.
*Corresponding author's E-mail: ishazafar1@gmail.com

ABSTRACT

Modern medical sciences have progressed a lot in its fight against aliments concerning heart. Day by day, the numbers of heart patients are increasing. A number of medications starting from Aspirin to sophisticated open heart surgeries are now a day's common in developed countries. In spite of the ultramodern technologies and the awareness programs, heart diseases like Angina pectoris and Myocardial Infarction are till today creating alarming situations in the society. If we consider the traditional herbal system of medicine in India- Ayurvedic, we will come to know that Ancient medical scientists have mentioned the remarkable cardio protective, heart muscle strengthening properties of *Terminalia arjuna* herb. Research shows *Terminalia arjuna* to be effective for a variety from heart related conditions similar to high blood pressure, heart palpitations, rapid heartbeat as well as high cholesterol. Studies attribute these features to certain tannins and glycosides that have specific antioxidant properties congenial for the cardiovascular system. Taken as brewed tea, powdered, or commercially prepared in tablet form, *Terminalia arjuna* has been used in hundreds of preparations along with other herbs to resolve an incredible number of health issues. Recommended by Ayurvedic practitioners as a liver tonic, *Terminalia arjuna* is known to regulate cholesterol by decreasing LDL levels in the liver. They are known to help in strengthening the heart muscles, relieving stress, and hypertension. *Terminalia arjuna* is also thought to fortify the central nervous system and also to quicken individual reflexes. Modern medicine corroborates that the herb is helpful in countering a range of cardiovascular disorders like large blood pressure, heart palpitations, rapid heartbeat and high cholesterol. Advocated by herbalists and Ayurvedic practitioners, the herb promotes healthy heart function.

Keywords: *Terminalia arjuna*, cardiovascular diseases, cholesterol.

INTRODUCTION

*T*erminalia arjuna is about 20-25 meters tall, deciduous tree found in many parts of the world. It has been reported by various scientist that leaves, shoot, fruit, bark, seed and other part of this plant are found useful in the treatment of many kind of diseases[1]. *Terminalia arjuna* is a well-known medicinal tree, the Indian physician Caraka and Susruta have mentioned this plant in their Samhitas. It contains a number of elements beneficial for human health, thus it has been used for centuries in the traditional medicine of India[2]. The medicinal importance of this tree is also well documented in Indian pharmacopeia, according to this its stem, bark and leaves possesses glycosides, large quantities of flavonoids, tannins and minerals. Flavonoids have been detected to exert antioxidant, anti-inflammatory and lipid lowering effects where as glycosides are cardiotonic, therefore making this plant distinctive amongst currently used medicinal plants[3]. Effect of this plant extract has also been studied on histopathology of Liver, Kidney and Pancreas of Alloxan-Induced diabetic rats. Pathological lesions were evoked in cells of diabetic rats. The extract improves the liver; kidney and pancreas function and reduce lesions associated with diabetic state in alloxan induced rats. The results of this study indicate that extract exhibit the protective effect on tissues and proves its potentials as an anti diabetic agent[4]. Evaluation of antioxidant Property of this plant provided efficacy by additive or synergistic activities because antioxidants from plant origin are essential to prevent the progression of free radical mediated disorders. Antioxidant, hypocholesterolaemic, apoptosis and cell cycle arrest effects of *Terminalia arjuna* methanolic extract (TAME) and *Terminalia arjuna* ethyl acetate extract (TAEAE) find out by using different *in-vitro* models[5]. Antimicrobial, antifungal activity of this plant has been found useful against pathogens causing infection. Organic extract obtained from this plant may be used to treat the bacterial and fungal infections, which has shown greater inhibition zones than the locally available herbal drops however, it need more detailed studies as *in vivo* testing and pharmacokinetics properties to establish the therapeutic utility of their plant extract in treating various diseases[6].

Over 80% of the world's deaths from CVDs occur in low- and middle-income countries. People in low- and middle-income countries are more exposed to risk factors such as tobacco, leading to CVDs and other non-communicable diseases. At the same time they often do not have the benefit of prevention programs compared to people in high-income countries. People in low- and middle-income countries who suffer from CVDs and other non-communicable diseases have less access to effective and equitable health care services which respond to their needs (including early detection services). As a result, many people in low- and middle-income countries die younger from CVDs and other non-communicable diseases, often in their most productive years. The poorest people in low- and middle-income countries are affected most. At the household level, sufficient evidence

is emerging to prove that CVDs and other non-communicable diseases contribute to poverty due to catastrophic health spending and high out of pocket expenditure. At macro-economic level, CVDs place a heavy burden on the economies of low- and middle-income countries. Non-communicable disease including cardiovascular disease and diabetes are estimated to reduce GDP by up to 6.77% in low- and middle-income countries experiencing rapid economic growth, as many people die prematurely, WHO[7]. Drug discovery and development aims to make available medications that should be safe and effective in improving the length of health and quality of life by making free from diseases. Therefore drug discovery and development process relies on the utilization of relevant methods, models, and validated biomarkers that are predictive of clinical effects in terms of diagnosis, prevention, therapy, and prognosis[8].

Development of effective drug may help million of patients affected by potentially life threatening diseases like Cardio Vascular Diseases, Central Nervous System Diseases, Immunological Diseases, Inflammatory Diseases, Infectious Diseases, Respiratory Diseases, Emerging and Reemerging Diseases to design and develop treatments for disorder that may influence the course of life threatening diseases. Therefore scientists are focusing on new strategies for the treatment of many diseases. The active molecule first isolated from the plants and then proceeds to new compounds by using semi synthetic process. The discovery and development of new medicines is a long and complicated process. Each success is built on many, many prior failures. Advances in understanding human biology and disease are opening up exciting new possibilities for breakthrough medicines. At the same time, researchers face great challenges in understanding and applying these advances to the treatment of disease. As our understanding of disease has increased to the extent that we know how disease and infection are controlled at the molecular and physiological level, scientists are now able to try to find compounds that specifically modulate those molecules, for instance via high throughput screening. Even more recently, scientists have been able to understand the shape of biological molecules at the atomic level, and to use that knowledge to design drug candidates.

Drug design involves the design of small molecules that are complementary in shape and charge to the bimolecular target with which they interact and therefore will bind to it.

Drug design, sometimes referred to as rational drug design or more simply rational design is the inventive process of finding new medications based on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a bio-molecule such as a protein, which in turn results in a therapeutic benefit to the patient. Drug design frequently but not necessarily relies

on computer modelling techniques. This type of modelling is often referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the bimolecular target is known as structure-based drug design. Structure-based drug design (or direct drug design) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy. If an experimental structure of a target is not available, it may be possible to create a homology of the target based on the experimental structure of a related protein. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist. Alternatively various automated computational procedures may be used to suggest new drug candidates. Drug design frequently but not necessarily relies on computer modeling techniques this type of modeling is often referred to as computer-aided drug design as described by[9]. Drug development phase involves rigorous testing and optimization of the selected compounds to identify the 'lead structure or candidate drug' which might be the most effective. Testing required by the health authorities is done in cells (*in vitro*) and in animals (*in vivo*) to study metabolism (pharmacodynamics and pharmacokinetics), safety, toxicity, dosage, and efficacy. The part of the development process in which the candidate drug obtained is thoroughly investigated, optimized, and prepared for testing in humans is referred to as the 'preclinical trial phase'. During the clinical phase of development, the efficacy and safety of the drug candidate is investigated in patients[10]. Computer Graphic Displays Molecular Modeling, the data produced are converted into visual image on the computer screen by graphic packages. These images may be displayed in a variety of styles like fill, CPK (Corey-Pauling- Koltum), stick, ball-stick, mesh-ribbon and color scheme with visual aids. Ribbon presentation is used for larger molecules like nucleic acid and protein. Using molecular mechanics, it is possible to generate a variety of different conformations by using a molecular dynamics program which 'heats' the molecule to 800-900K. The program allows the structure to undergo bond stretching and bond rotation if it is being heated[11]. The molecular structure of plant derived drugs have been studied by using advance molecular techniques such as X- rays crystallography[12].

In the present scenario semi synthesis or partial chemical synthesis is a type of chemical synthesis that uses drugs which are isolated from natural sources, then chemically modified in a laboratory to make the drugs more effective, longer lasting, easier to administer, and less toxic to the patient.

Our research and development work will be based on latest pharmaceutical technology and therapeutic platforms to identify and validate novel active molecules from extract of *Terminalia arjuna*.

Drug Development and cardiovascular Potential of *Terminalia arjuna*

Terminalia arjuna has been reported to contain several bioactive compounds. Many experimental studies have reported its anti-ischemic, antihypertensive, antihypertrophic effects, which have relevance to its therapeutic potential in cardiovascular diseases in humans. Several clinical studies have reported its efficacy mostly in patients with ischemic heart diseases, hypertension and heart failure. However, a major short coming in all these experimental and clinical studies is poor in term of design and method used for generating safety data. The research has addressed all issues for a scientific validation of this medicinal plant[15].

Although a number of chemical compound have been isolated from *Terminalia arjuna*, only a few of them have been evaluated for their biological activity. As a part of drug discovery program for cytotoxic agents from Indian medicinal plants, four novel cytotoxic agents arjunic acid (1), arjungenin (2), arjunetin (3) and arjunoglucoside I (4) have been isolated from the bark of *T.arjuna* by different group of scientist. Out of the four compounds, arjunic acid (1) was significantly found active against the human oral, ovarian and liver cancer cell lines. Further, the most active compound arjunic acid was converted into seven semi-synthetic ester derivatives 5 - 11. 2-O-Palmitoyl arjunic acid (6) which strength/activity showed two times more active, while 2, 3-di-O-acetyl-, 2-O-p-anisoyl-, 2, 3-di-O-benzoyl- and 2, 3-di-O-p-nitrobenzoyl arjunic acid (7 - 10) showed 1.7 - 2.3 times less activity than the cytotoxic drug vinblastine against the liver cancer cell lines HepG-2 and WRL-68 respectively[16].

Cardiovascular diseases are the major cause of death throughout the world including India; it claims more lives than all other diseases combined. Worldwide it is estimated that more than 12 million people die every year from cardiovascular disease. Cardiovascular disease involves the heart and its two networks of blood vessels, the system which circulates the blood throughout the body and the system which circulates the blood through the lungs[17].

Pharmaceutical companies have to make sure that only safe and effectual medications should be released to the public. Discovery of any New Medication, Pharmacologist, Chemist and other scientists, working in laboratories, pinpoint genetic and cellular properties are tested as different parameter methods. They then introduced biological and or chemical elements hoping to understand the adverse effect on the various animal and finally on the diseased cell. Following preclinical evaluations, of all the essential test and discoveries are carried out accordingly, it is recommended that only 0.001% (5 out of 5000) is considered safe for human consumption and is tested on volunteers. Testing in patients continues for an additional three to six years, until one of the initial 5000 (0.0002%) is chosen and approved for public consumption as a new medicine. In the drug discovery process identify

a suitable target first. This is a molecule or a protein receptor that is specifically associated with a disease condition or pathology. For this purpose, it is important to understand how the disease occurs at the molecular, cellular, and genetic levels. Once a target is identified, the next step involves understanding how the target plays a role in the disease process. This is followed by testing of the target against different known and new molecule obtained from medicinal plant, microorganisms to identify either one or several 'lead molecule' which interact with the target and show the potential to either neutralize or slow the disease process[18].Drug candidates, discovered in academic and pharmaceutical/biotech research labs, are tested for their interaction with the drug target. Up to 5,000 to 10,000 molecules for each potential drug candidate are subjected to a rigorous screening process which can include functional genomics and/or proteomics as well as other screening methods. Once scientists confirm interaction with the drug target, they typically validate that target by checking for activity versus the disease condition for which the drug is being developed. After careful review, one or more lead compounds are chosen[19]. When the candidate molecule shows promise as a therapeutic, it must be characterized—the molecule's size, shape, strengths and weaknesses, preferred conditions for maintaining function, toxicity, bioactivity, and bioavailability must be determined. Early pharmacological studies help to characterize the underlying mechanism of action of the compound. Drug formulation and delivery may be refined continuously until, and even after, the drug's final approval. Scientists determine the drug's stability—in the formulation itself, and for all the parameters involved with storage and shipment, such as heat, light, and time. The formulation must remain potent and sterile; and it must also remain safe**.** Pharmacokinetic studies provide useful feedback for formulation scientists. Pharmacokinetic studies yield parameters such as area under the curve, maximum concentration of the drug in blood, and time at which maximum concentration is reached. Later on, this data from animal Pharmacokinetic studies is compared to data from early stage clinical trials to check the predictive power of animal models.

Steps involved in drug designing, first acquired knowledge about active site that needs to be attacked by the drug and then utilized this information to design a drug. This drug will not only bind to the chosen site but will also possess all other properties required of a drug. Therefore, drug designing will involve at least three steps:

1. Knowledge will have to be acquired about the site structure, up to the level of atomic resolutions, so that the accessible surface, which need to be attacked, to be known.

2. A ligand will have to be designed that will fit the binding site; for this purpose the steric outline of the ligand should be complementary to the active site and, therefore this complementary feature will have

to be built in the ligand at appropriate positions. This should result in the maximum interactions between the atom of the ligand and the site, and is mainly achieved with the help of computer aided methods.

3. Once the ligand is designed to fit the binding site, ligand needs to be modified to have pharmacological properties, while mentaining its affinity for the binding site. This and the above steps (ll) will require three dimensional contractions, so that computer-based modelling can be used for automated site-directed drug designing Pacific Bio Labs. Preclinical testing analyzes the bioactivity, safety, and efficacy of the formulated drug product.[20] This testing is critical to a drug's eventual success and, as such, is scrutinized by many regulatory entities.

During the preclinical stage of the development process, plans for clinical trials and an Investigative New Drug (IND) application are prepared. Studies taking place during the preclinical stage should be designed to support the clinical studies that will follow .The main stages of preclinical toxicology testing are: Acute Studies, Acute toxic studies look at the effects of one or more doses administered over a period of up to 24 hours. The goal is to determine toxic dose levels and observe clinical indications of toxicity. Usually, at least two mammalian species are tested. Data from acute toxic studies helps to determine doses for repeated dose studies in animals[21].

1. **Phase I**: Initial stage of testing safety trials on a new medicine. A small group of 20–100 healthy volunteers will be recruited. An attempt is made to establish the dose range tolerated by volunteers for single and for multiple doses. Phase I trials are sometimes conducted in severely ill patients (e.g., in the field of cancer) or in less ill patients when pharmacokinetic issues are addressed. Pharmacokinetic trials are usually considered Phase I trials regardless of when they are conducted during a medicine's development.

2. **Phase II**: Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indication in patients with the disease and condition. This phase of testing also helps to determine the common short term side effect and risks associated with the drug. Phase two studies are typically well controlled, closely monitored and conducted in a relatively small number of patients. In some studies it is clearly mentioned that in few trial cases it may involves several hundred people to set the effectiveness of the newly synthesized drug and its adverse effects.

3. **Phase III**: Phase 3 studies are expended controlled and uncontrolled trails. They are performed after preliminary evidence suggesting effectiveness of the drug which has been obtained in phase ll and are intended together the additional information about effectiveness and safety that is needed to evaluate the overall benefit – risk relationship of the drug .Phase III study also Provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labelling. Phase three study include several hundred to several thousand people.

4. **Phase IV**: also known as post marketing surveillance which is also carried out once the drug is approved and marketed. The aim of phase IV is to find out safety profile in large patient pool across the world and to establish the safety profile of the drug[22].

CONCLUSION

An analysis of the origin of the drugs developed between 1981 and 2002 showed that natural products or natural product-derived drugs comprised 28% of all new chemical entities (NCEs) launched onto the market. In addition, 24% of these NCEs were synthetic or natural mimic compounds, based on the study of pharmacophores related to natural products. This combined percentage (52% of all NCEs) suggests that natural products are important sources for new drugs and are also good lead compounds suitable for further modification during drug development. The large proportion of natural products in drug discovery has stemmed from the diverse structures and the intricate carbon skeletons of natural products. Since secondary metabolites from natural sources have been elaborated within living systems, they are often perceived as showing more "drug-likeness and biological friendliness than totally synthetic molecules, making them good candidates for further drug development. Scrutiny of medical indications by source of compounds has demonstrated that natural products and related drugs are used to treat 87% of all categorized human diseases, including as antibacterial, anticancer, anticoagulant, antiparasitic, and immunosuppressant agents, among others. There was no introduction of any natural products or related drugs for 7 drug categories (anesthetic, antianginal, antihistamine, anxiolytic, chelator and antidote, diuretic, and hypnotic) during 1981 to 2002.

Terminalia arjuna, have a long history of use in the treatment of human diseases. This plant is still in use today for the treatment of various diseases as ingredients of official drugs or herbal preparations used in systems of traditional medicine. 2-O-Palmitoyl arjunic acid , a semi-synthetic derivative of arjunic acid cytotoxic drug obtained from *Terminalia arjuna*, is prescribed for the treatment of liver cancer cell lines in various countries. But in our literature survey of *Terminalia arjuna* the leaves were found to be virgin regarding drug discovery and development and very little work is regarding its chemistry has been reported however these leaves are extensively folklore medicine to treat many diseases. There is no data reference available regarding drug discovery and development of drug from *Terminalia*

arjuna plant extracts specially work on leaves of this plant is very scanty.

This research and development work will be based on latest pharmaceutical technology and therapeutic platforms to identify and validate novel active molecules from *Terminalia arjuna.*

REFERENCES

1. Aggarwal, M.R. Agarwal, S. Rajpal: Method of plant analysis. Phytochemical Methods, A guide to modern technique of plant analysis 3rd ed. Ltd, London, 43, 2009, 1-33.

2. Ascherio, Dietary iron intake and risk of coronary disease among men. Circulation, 89, 3, 2007, 969-74.

3. Ascherio, Trans-fatty acids intake and risk of myocardial infarction. Circulation, 89, 1, 2012, 94-101.

4. Biller, Custer, Dickinson, Durham, Gavai, Hamann, Josephs, Moulin, Pearl, Flint, Sanders, Tymiak, Vaz: The Challenge of quality in candidate optimization in Pharmaceutical Profiling in Drug Discovery for Lead Selectio. AAPS Press 2008; 413-429.

5. Chaudhari M., Mengi S: Evaluation of phytoconstituents of Terminalia arjuna for wound healing activity in rats. Phytotherapy Research, 20, 2006, 799–805.

6. Feher M, Schmidt JM: Property distributions: differences between drugs, natural products and molecules from combinatorial chemistry. j chem inf comput sci, 43, 1, 2003, 218–27.

7. Feldman, Elaine B. and Kuske. Drug discovery and development, 56, 9, 2008, 60-71.

8. Field MJ, Boat TF. Rare Diseases and Orphan Products: Accelerating Research and Development. National Academies Press (US); 2010.

9. Gupta, Steps involved in drug designing. Drug discovery and development, 8, 2011, 56-59.

10. Gupta L.P., Sen S.P., Udupa K.N: Pharmacological studies on Terminalia arjuna. Journal of Research in Indian Medicine, Yoga and Homeopathy, 11, 1976, 16–24.

11. Hamann, Penzotti, Landrum, Putta: Building predictive ADMET models for early decisions in drug discovery. Current Opinion in Drug Discovery & Development, 7, 2004, 49-60.

12. Harborne JB: Method of plant analysis. Phytochemical Methods , A guide to modern Technique of Plant Analysis 3rd ed. Chapman and Hall Ltd., London, 2008, 1-33.

13. Indian Herbal Pharmacopoeia. A Joint Publication of RRL Jammu-Tawi and Indian Drug Manufacturing Association, Mumbai 2009, 2.

14. Kamal Rai Aneja[I], Chetan Sharma[II], Radhika Joshi[III]. Braz. j. otorhinolaryngol; vol.78 no.1 São Paulo Jan./Feb, 2012.

15. Kapetanovic, Pharmaceutical profiling in drug discovery. Drug Disc. Today, 8, 2011, 316-323.

16. Kennedy T: Managing the drug discovery and development interface. Drug Discovery Tech, 2, 2011, 436-441.

17. Kumar DS, Prabhakar YS.V: Pharmacological investigation on Terminalia arjuna Planta Medica, 28, 2, 2008, 175-177.

18. Landrum : The influence of drug-like concepts on decision-making in medicinal chemistry. Nat. Rev. Drug Disc, 6, 11, 2009, 881–890.

19. Lihong, Serum cholesterol in young men and subsequent cardiovascular disease. The New England Journal of Medicine, 328, 5, 2007, 313-17.

20. Matthias, Hopkins, Groom, and Alexander. Ligand efficiency: a useful metric for lead selection. Drug Discovery Today, 9, 10, 2011, 430–431.

21. Maulik SK[1], Talwar KK: Therapeutic potential of Terminalia arjuna in cardiovascular disorders; 2007.

22. National Research Council (US) Committee on Research Opportunities in Biology.

23. Nitish Chhabra, Seth Bihani GL and Sudeep Bhardwaj: Introduction to Various Stages in Process of Drug Development.

24. Palash Das: Detailed Stages of Drug Development; 2012.

25. Praveen Kumar P*1, Prabhakara MC1, Satyavathi K2, Anil Kumar S1. Evaluation of cardiac activity of some traditionally used backyard Indian medicinal plants.

26. Radhakrishnan R., Wadsworth R.M., Gray, and A.I.: Terminalia arjuna, ayurvedic cardiotonic, increases contractile force of rat isolated atria. Phytotherapy, 1993, 266–268.

27. Ragavan* and S. Krishnakumari: Antidiabetic effect of t. arjuna bark extract in alloxan induced diabetic rats. Indian Journal of Clinical Biochemistry; 21, 2, 2006, 123-128.

28. R. Ashok Raj: A recent technology in drug discovery and development, 2, 1, 2012, 22-39.

29. Saxena M, Faridi U, Mishra R, Gupta MM, Darokar MP, Srivastava SK, Singh D, Luqman S, Khanuja SP. Cytotoxic agents from Terminalia arjuna; 2011.

30. Singh N, Kapoor KK, Singh SP, Shankar K, Sinha JN, Kohli RP. Mechanism of cardiovascular actions of Terminalia arjuna. Planta med; 45, 1982, 102-104.

31. Shridhar Dwivedi: Terminalia arjuna A useful drug for cardiovascular disorders Preventive Cardiology Group, University College of Medical Sciences, University of Delhi, Delhi 110095, India.

32. S S Savrikar* and B Ravishankar: Introduction to 'Rasashaastra' the Iatrochemistry of Ayurveda, 8, 5, 2011, 66–82.

33. Stampfer, Vitamin E consumption and the risk of coronary disease in women. The New England Journal of Medicine, 328, 20, 2008, 1444-49.

34. Stampfer, Tymiak, Roberts, SA: Drug metabolism and pharmacokinetics in drug discovery. Current Opinion in Drug Discovery and Development, 6, 2010, 66-80.

35. Tanushri Patnaik: Isolation of triterpenoids glycosides from bark of terminalia arjuna using chromatographic technique & investigation of pharmacological behavior upon muscle tissue. E- Journals of chemistry, 4, 4, 2007, 474-469.

36. Teresa brodniewicz1 and Grzegorz grynkiewicz: Preclinical drug development. Acta Poloniae Pharmaceutica ñ Drug Research, 67, 6, 2010, 579-586.

37. Wang, H, Adedoyin: Drug discovery integration of experimental and computational technologies. Drug Discovery Today, 8, 2009, 852-861.

Source of Support: Nil, **Conflict of Interest:** None.