

*Review Article***Cardiovascular Pharmacology for the Past 5 Years in India**

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Over the last five years, cardiovascular pharmacology research has maintained its drive in both academia and industry in India. Academic research in both governmental and private institutes have been quite active and so were various government research laboratories. As pharmaceutical industries have been mostly involved in clinical trials with cardiovascular drugs, very few have also engaged in research and development of new molecules. Cardiovascular pharmacology research in India has been mostly centred around drugs for dyslipidemias, with a couple of breakthroughs. Anti-ischemic drugs and drugs for heart failure have also been given due priorities. Academic research which has a rich tradition in India, has been able to produce useful scientific resources and of late has realised the need for academia-industry research partnership to carry out meaningful research. In consonance with the heritage of rich traditional medicine, cardiovascular pharmacologists in India have been involved in both pre-clinical and clinical validation of the traditional drugs with active governmental support.

Keywords: Dyslipidemias; Ischemic Heart Disease; Hypertension; Animal Research; Clinical Trials; Herbal Medicine

Introduction

Cardiovascular diseases (CVDs) are leading causes of disability and death in India, accounting for a quarter of all mortality (Prabhakaran *et al.*, 2016). Ischemic heart disease and stroke are responsible for >80% of CVD deaths. The Global Burden of Disease study estimate of age-standardized CVD death rate is 272 per 100 000 population in India against the global average of 235 per 100 000 (Yusuf *et al.*, 2015). Some characteristics of the CVD in India are particular causes of concern, including its faster growth, the early age onset, and the high case fatality rate. In India, there is an epidemiological transition from predominantly infectious disease conditions to non-communicable diseases. Although there is a wide heterogeneity in the prevalence of cardiovascular risk factors across different regions of our country, CVD has emerged as the leading cause of death across India, irrespective of the socioeconomic status and geographical areas. People belonging to lower socioeconomic backgrounds often do not receive optimal therapy, leading to poorer outcomes. Countering the public health issue needs the

development of multipronged strategies, such as the design and effective implementation of evidence-based policy, reinforcement of health systems, and emphasis on prevention, early detection, and treatment with the use of both conventional and innovative techniques. Effective drug development policies for prevention and cure constitute an integral part of the whole exercise.

Cardiovascular segment is the largest therapeutic segment in the global drug development process. Research and development programme in drug discovery can not thrive without a steady input of human resources for both bench and bedside. India being a leader in human resources has been contributing consistently for decade a long time.

Trend of Academic Research in CV Pharmacology in India in the Last 10 Years

Cardiovascular pharmacology has been a major area of research in many academic institutions and government research laboratories, like All India Institute of Medical Sciences, New Delhi; JIPMER, Puducherry; KGMC, Lucknow; CDRI, Lucknow;

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Seth GS Medical College, Mumbai; MS University, Vadodara; DIPSAR, New Delhi; NIPER, Mohali, etc. for the last many decades. The major pharmacological properties studied included cardiac inotropic effects, acute and chronic antihypertensive effects (Jain *et al.*, 2017, Dey *et al.*, 2016, Choudhary and Bodakhe, 2016), anti-ischemic effect (Dhivya *et al.*, 2017, Rana *et al.*, 2015, cardiac ischemic reperfusion injury (Suchal *et al.*, 2017; Randhawa and Jaggi, 2016; Charan *et al.*, 2015), hypolipidemic effects (Subbaiah *et al.*, 2017; Rai and Dhaneshwar, 2015) and cardiac hypertrophy and failure (Kumar *et al.*, 2017; Maulik *et al.*, 2012) using various animal models, from higher to lower mammals. Very few laboratories in India have actually ventured into studies involving antiarrhythmic studies, because of the high technicalities of the study methods.

Most of the studies stressed on the hemodynamic and biochemical studies of the whole animal to demonstrate the effects of known and unknown compounds.

Slowly over the last few years, owing to the stricter control over animal experiments with higher mammals, the researchers had to switch over to lower mammals (rodents). The study parameters also shifted to more of molecular biology, genomics and proteomics (Punchaichira *et al.*, 2016; Biswas *et al.*, 2014). Hemodynamic studies took a back seat due to difficult procedures in small animals.

With the advent of technological advancements, mostly in the field of cardiovascular imaging, quite a few academic and government research laboratories, due to liberal funding policies and opportunities, took advantage of it and embarked on various other disease models, like cardiac hypertrophy and cardiac failure. Even MRI studies were available in animal research which helped in ischemic pathology research (Chauhan *et al.*, 2012)

Research involving isolated tissues and cell lines also took a centre stage either as a primary research area or supplementary source of evidence of efficacy studies of potential molecules in whole body (Thakur *et al.*, 2015). In this respect, atherosclerosis research has been a central activity of many laboratories, particularly CDRI, which have received international commendation (Kesavan *et al.*, 2016).

In AIIMS, New Delhi both basic and clinical research in cardiovascular pharmacology has been a practice for a long time. It has been possible due to a legacy of a strong research collaboration between pharmacologists and cardiologists. In this venture, pathologists and molecular biologists have also been contributing to a large extent. This is an ideal condition for meaning pharmacology research.

If publication is an index of research activity (because negative results are rarely published), a simple pubmed MeSH search with words “cardiovascular pharmacology” and “India” shows a huge increase in cardiovascular pharmacology research in India, with a steadily increasing number (Figs. 1 and 2) over the last 50 years.

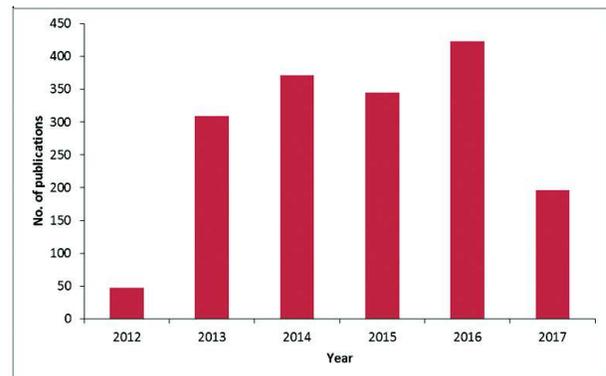


Fig. 1: Publications in Cardiovascular Pharmacology from India for the last 5 years

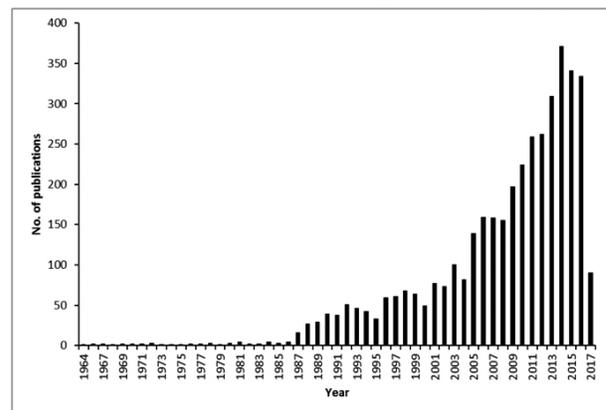


Fig. 2: Publications in Cardiovascular Pharmacology from India for the last 50 years

Why Should Academia Engage Themselves in Drug Development Research?

The research pursuit in the field of cardiovascular

pharmacology in academic institutions may be largely attributed, in my opinion, to the personal interest and training of the faculty members and passing the legacy to their students who in turn have tried to develop similar laboratories in smaller medical colleges with rather poorer funding opportunities.

But if someone asks why academic institutes should engage themselves in it, a simple and straightforward answer will be to develop human resources, required for ever demanding research and development activities in pharmaceutical industries both in India and abroad. The process although has been always a passive one, has been largely successful.

In addition to it, Medical Council of India has made it mandatory for the faculty members to have publications as a major component of assessment for career advancement. Research is the only way; a faculty in pharmacology can accomplish it.

Are Academia Nurseries for Researchers in Industry?

In fact, academia can be termed as ‘nursery’ for the researchers for industry. This in a way acts as symbiosis between the two systems which should be acclaimed. In fact, this should be encouraged at the academic institutions to expose the post graduate students to the industry need for pharmacology research, including cardiovascular pharmacology. The academia is benefitted by learning the translational opportunities of their research activities and thus become highly motivated research. Many institutions have begun to appreciate it and have started getting benefitted.

Does Industry Promote Research on Cardiovascular Pharmacology?

Industry does not put stake in ‘blue sky research’ and why should they? But of course, many a times, many industries outsource the knowledge and expertise in its drug development programmes in academic institutes, with good track record. It can be considered as research promotional activities and has been a practice for the last couple of years.

The most notable drug discovery by any Indian Pharmaceutical company (Zydus) in the last five years is saroglitazar. The first dual PPAR agonist.

Saroglitazar provides safe and effective alternative for the treatment of diabetic dyslipidemias.

Otherwise, industries are involved mostly in multicentre and multinational clinical trials with drugs developed outside India.

Present Priorities of Cardiovascular Pharmacology Research in Academia and Research Laboratories in India?

The global CV pharmacology research activities are stupendous, both at the academic and industry levels. Indian contribution to it, both at the pre-clinical (some prefer the term non-clinical) and clinical stages is considerable, due mainly to the available trained scientists and clinicians in India.

Multi-national Companies (MNCs) have their research laboratories in India which cater to the global need. All these scientists working here are mostly the products of our academic institutes. In this process, India is being benefitted both in terms of job opportunities and control of national health needs.

But the question remains, whether this research caters to basic cardiovascular disease burden of India. The answer is by and large yes, although some CV diseases unique to India, like drug development for rheumatic heart disease have never been the research priorities either of any industry or academia.

Recently over the last decade or so, there has been a resurgence of research interest in genomic and proteomic research in CV diseases in India mostly restricted to epidemiological research. Pharmacogenomic research has not been very extensive across the country, except for JIPMER, Puducherry which had taken a lead in this area (Kumar *et al.*, 2015 and Umamaheswaran *et al.*, 2015)

Indian System of Medicine and Cardiovascular Pharmacology Research in India

There has been a great boost in promotion of ISM at the governmental level over the last few years. Pharmacological validation of claims in classical texts and practices has been a priority area of research in AYUSH. ISM drugs are mostly favoured in non-communicable disease conditions, of which CV diseases are a major component. Naturally, both in the pre-clinical and clinical validation, pharmacologists

are playing a pivotal role. Standardised herbal medicine, both belonging to classical text and non-codified ones are being widely screened for their various cardiovascular effects across the country in several academic institutes with active support of Ministry of AYUSH (Maulik and Talwar, 2012, Dwivedi and Chopra, 2014, Maulik and Katiyar, 2010). More importantly, randomised clinical trials are being carried out in modern medicine institutions with these drugs in various CV diseases in which cardiovascular pharmacologists are playing an active role in design and conduct (Maulik *et al.*, 2016).

Contribution in Regulatory Affairs

Pharmacologists are playing an integral role in various technical committees of CDSCO. Those with cardiovascular research experience are contributing to major policy decisions in an effective manner.

Participation in Ethics Committees

As cardiovascular drugs constitutes majority of multicentre trials in India, and a pharmacologist plays an essential role in all ethics committees, those with basic and clinical cardiovascular pharmacology expertise can contribute to great in decision making on project approval, adverse effect monitoring, reporting, causality assessment etc.

References

- Biswas A, Rao VR, Seth S and Maulik S K (2014) Next generation sequencing in cardiomyopathy: towards personalized genomics and medicine *Mol Biol Rep* **41** 4881-4888
- Charan K, Goyal A, Gupta J K and Yadav H N (2016) Role of atrial natriuretic peptide in ischemic preconditioning-induced cardioprotection in the diabetic rat heart *J Surg Res* **201** 272-278
- Chauhan A, Sharma U, Reeta K H, Jagannathan N R, Mehra RD and Gupta Y K (2012) Neuroimaging, biochemical and cellular evidence of protection by mycophenolate mofetil on middle cerebral artery occlusion induced injury in rats *Eur J Pharmacol* **684** 71-78
- Choudhary R and Bodakhe S H (2016) Olmesartan, an angiotensin II receptor blocker inhibits the progression of cataract

Projected Priority Research Areas in Academia and Research Laboratories

Government of India has laid emphasis on the overall availability of trained personnel for health research from medical colleges across the country through scholarships, fellowships and career advancement scheme etc. for faculty and young medical doctors and other scientists to take up medical and health research as a career.

Other priority areas have been the creation of a cadre of trained medical/health researchers in specific identified priority areas of health research viz., Clinical Trials; Toxicology; Good Clinical Practices (GCP); Good Laboratory Practices (GLP); Quality Control (QC); Genomics; Proteomics; Biotechnology; Stem cells; Genetics; Drugs chemistry; and operational research etc.

Government encourages to create, support, nurture and encourage the trainees from these medical colleges to forge linkages with other scientists from universities, research institutes etc. to develop multidisciplinary and multi-sectoral teams necessary for addressing critical national and local health problems. [Source: Government of India, Department of Health Research (Ministry of Health and Family Welfare)].

This will definitely boost research activity in cardiovascular pharmacology in coming years.

formation in cadmium chloride induced hypertensive albino rats *Life Sci* **167** 105-112

- Dey S K, Prabhakar P, Saini M, Joseph T, Thelma B K, Maulik S K and Kundu S (2016) Inhibitors of dopamine- β -hydroxylase obtained by structure based methods exhibited anti-hypertensive effect in l-name induced hypertensive rats *J Hypertens* **34** Suppl 1 - ISH 2016
- Dhivya V, Priya L B, Chirayil H T, Sathiskumar S, Huang C Y and Padma V V (2017) Piperine modulates isoproterenol induced myocardial ischemia through antioxidant and anti-dyslipidemic effect in male Wistar rats *Biomed Pharmacother* **87** 705-713
- Dwivedi S and Chopra D (2014) Revisiting *Terminalia arjuna* - An ancient cardiovascular drug *J Tradit Complement Med* **4** 224-231

- Jain M, Bhosale V, Tripathi D, Singh H, Pal N, Hanif K and Jagavelu K J (2017) Antihypertensive drugs aliskiren, nebivolol, and olmesartan reduce hypertension by reducing endothelial microparticle and regulating angiogenesis *J Cardiovasc Pharmacol* 2017 May 9
- Jaiswal A, Kumar S, Seth S, Dinda A K and Maulik S K (2010) Effect of U50,488H, a κ -opioid receptor agonist on myocardial α - and β -myosin heavy chain expression and oxidative stress associated with isoproterenol-induced cardiac hypertrophy in rat *Mol Cell Biochem* **345** 231-240
- Kesavan R, Chandel S, Upadhyay S, Bendre R, Ganugula R, Potunuru U R, Giri H, Sahu G, Kumar P U, Reddy G B, Joksic G, Bera A K and Dixit M (2016) Gentiana lutea exerts anti-atherosclerotic effects by preventing endothelial inflammation and smooth muscle cell migration *Nutr Metab Cardiovasc Dis* **26** 293-301
- Krishna Kumar D, Shewade DG, Lorient M A, Beaune P, Sai Chandran B V, Balachander J and Adithan C (2015) An acenocoumarol dosing algorithm exploiting clinical and genetic factors in South Indian (Dravidian) population *Eur J Clin Pharmacol* **71** 173-181
- Kumar S, Jahangir Alam M, Prabhakar P, Ahmad S, Maulik S K, Sharma M and Goswami S K (2017) Proteomic analysis of the protective effects of aqueous bark extract of *Terminalia arjuna* (Roxb.) on isoproterenol-induced cardiac hypertrophy in rats *J Ethnopharmacol* **198** 98-108
- Maulik S K and Talwar K K (2012) Therapeutic potential of *Terminalia arjuna* in cardiovascular disorders *Am J Cardiovasc Drugs* **12** 157-163
- Maulik S K, Prabhakar P, Dinda A K and Seth S (2012) Genistein prevents isoproterenol-induced cardiac hypertrophy in rats *Can J Physiol Pharmacol* **90** 1117-1125
- Maulik S K, Wilson V, Seth S, Bhargava B, Dua P, Ramakrishnan S and Katiyar C K (2016) Clinical efficacy of water extract of stem bark of *Terminalia arjuna* (Roxb. ex DC.) Wight & Arn. in patients of chronic heart failure: a double-blind, randomized controlled trial *Phytomedicine* **23** 1211-1219
- Prabhakaran D, Jeemon P and Roy A (2016) Cardiovascular diseases in india: current epidemiology and future directions *Circulation* **133** 1605-1620
- Punchaichira T J, Prasad S, Deshpande S N and Thelma B K (2016) Deep sequencing identifies novel regulatory variants in the distal promoter region of the dopamine- α -hydroxylase gene *Pharmacogenet Genomics* **26** 311-323
- Rai H and Dhaneshwar S S (2015) Amide-linked ethanolamine conjugate of gemfibrozil as a profound HDL enhancer: design, synthesis, pharmacological screening and docking study *Curr Drug Discov Technol* **12** 155-69
- Rana A, Goyal N, Ahlawat A, Jamwal S, Reddy BV, Sharma S. (2015) Mechanisms involved in attenuated cardio-protective role of ischemic preconditioning in metabolic disorders *Perfusion* **30** 94-105
- Randhawa P K and Jaggi A S (2017) A review on potential involvement of TRPV1 Channels in ischemia-reperfusion injury *J Cardiovasc Pharmacol Ther* 2017 Jan 1
- Subbaiah G V, Mallikarjuna K, Shanmugam B, Ravi S, Taj P U and Reddy K S (2017) Ginger treatment ameliorates alcohol-induced myocardial damage by suppression of hyperlipidemia and cardiac biomarkers in rats *Pharmacogn Mag* **13** S69-S75
- Suchal K, Malik S, Khan S I, Malhotra R K, Goyal S N, Bhatia J, Ojha S and Arya D S (2017) Molecular pathways involved in the amelioration of myocardial injury in diabetic rats by kaempferol *Int J Mol Sci* 18
- Thakur A, Alam M J, Ajayakumar M R, Ghaskadbi S, Sharma M and Goswami S K (2015) Norepinephrine-induced apoptotic and hypertrophic responses in H9c2 cardiac myoblasts are characterized by different repertoire of reactive oxygen species generation *Redox Biol* **5** 243-252
- Umamaheswaran G, Praveen R G, Damodaran S E, Das A K and Adithan C (2015) Influence of SLC22A1 rs622342 genetic polymorphism on metformin response in South Indian type 2 diabetes mellitus patients *Clin Exp Med* **15** 511-517
- Yusuf S, Wood D, Ralston J and Reddy K S (2015) The World Heart Federation's vision for worldwide cardiovascular disease prevention *Lancet* **386** 399-402.