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Developing Novel Anti-Diabetic Drugs for Geriatric Population: Prospecting for Lead compounds among Botanical Formulations of Traditional Medicine

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ABSTRACT

Diabetes has attained pandemic proportions since decades and the trend of its spread shows no sign of receding. Other than high morbidity and mortality, diabetes and its complications causes tremendous cost to the individual, family, and governments. Definite causes of diabetes are not defined though there are numerous pathways described as leading to the destruction of beta cells in the pancreas and development of insulin resistance. Single agents and combination therapies are able to achieve target glycemic goals for limited periods of time and only in a subset of patients with Type 2 Diabetes Mellitus. There is renewed interest in multi-ingredient synergistic formulations for management of polygenic syndromes and conditions like diabetes. Drug discovery and development should be explored among rationally designed, carefully standardized, synergistic traditional herbal formulations and botanical drug products with robust scientific evidence. There are many Ayurvedic drugs available in the Indian market, claiming effective management for diabetes. Drug discovery is a process involving humongous cost, effort and time. Any lead followed in this direction needs to be selected with great scrutiny and caution.

KEYWORDS

Diabetes Mellitus

Ayurveda

Traditional Medicine

Botanical Drugs

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DIABETES MELLITUS: THE PANDEMIC

Sir Michael Hirst in his foreword to the sixth edition of IDF Diabetes Atlas notes, "By the end of 2013, diabetes will have caused 5.1 million deaths and cost USD 548 billion in healthcare spending. Without concerted action to prevent diabetes, in less than 25 years' time there will be 592 million people living with the disease. Most of those cases would be preventable"¹. In 2013 there were 382 million people with diabetes, and this is expected to rise to 592 million by 2035¹. The world prevalence of diabetes among adults (aged 20–79 years) was 6.4%, affecting 285 million adults, in 2010, and will increase to 7.7% and 439 million adults by 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries. These predictions, based on a larger number of studies than previous estimates, indicate a growing burden of diabetes, particularly in developing countries².

With the increase in number of T2DM patients, has increased the number of cases of diabetic vascular complications. Chronic diabetic complications are the major cause of morbidity and mortality among patients with diabetes. The longer lifespan of patients with both type 1 and type 2 diabetes resulting from improvements in diabetes management has also allowed the chronic complications to manifest as patients age. Microvascular (neuropathy, nephropathy, and retinopathy) and macrovascular complications (accelerated atherosclerosis, heart attacks and stroke) are a major cause of loss of life and productivity in these patients³. 23.7% of T2DM patients in South India suffer from Retinopathy, where as 5.5% suffers from Nephropathy and 27.5% from Peri-neuropathy.

Among the same population, 38% suffer from Hypertension, which is the major Macrovascular complication, followed by 11.4% suffering from cardiovascular disease, 4% with Peripheral vascular disease and 0.9% from Cerebrovascular accidents. Other than increasing morbidity and death, diabetes increases the financial burden on the sufferers by 17.5% for inpatient care, 7.7% for outpatient care and 16.3% in cases requiring surgical care, in comparison to non-diabetics seeking medical interventions for similar morbidities⁴.

CURRENT APPROACHES TO TYPE 2 DIABETES MELLITUS:

"During the past decade, improved understanding of the role of adipose tissue, the brain and the gastrointestinal tract in the pathophysiology of type 2 diabetes mellitus (T2DM) has resulted in the development of many new classes of anti-diabetic agents, which has led to revolutionary changes in the treatment of patients with T2DM"⁵. Current therapies in management of T2DM include life style modifications, drug regimens and surgical options.

None of the currently available pharmacologic agents used to treat patients with T2DM has been demonstrated to stop the progressive decline of pancreatic β -cell function and insulin secretion. Consequently, single agents and combination therapies are able to achieve target glycemic goals for limited periods of time and only in a subset of patients with T2DM.

Theoretically, insulin preparations should be able to lower HbA1c in patients with T2DM to any desired level. However, the non-physiologic route of administration and the prolonged duration of action of the available insulin preparations, coupled with the large doses needed to overcome insulin resistance, preclude mimicking physiologic insulin secretion. The incidence of moderate and severe hypoglycemia increases progressively as insulin treatment regimens aim to reduce the level of HbA1c from 7.5% to 6.0%. Progressive weight gain that might exceed 10 kg is associated with increasingly intensive insulin treatment⁵.

Moreover, current therapies do not address the pathologies of vascular complications of T2DM. They deal with the results of these progressive comorbidities such as retinal bleeds and cardiac failures. While explaining the unifying mechanism of hyperglycemia-induced cellular damage, in Brownlee observes that while microvascular disease end points shows tenfold increase in risk as HbA1c increases from 5.5 to 9.5%, the macrovascular risks increases only about twofold. It is now acknowledged that insulin-resistance and metabolic syndrome play a major role in macrovascular risks.

So much so that after adjustment for 11 known cardiovascular risk factors, including Lipid profile, Hypertension, and smoking, the insulin-resistant subjects still holds a twofold increased risk of cardiovascular disease. This reflects direct causal

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relationship of insulin resistance to cardiovascular risk, which was previously unappreciated⁶.

Other than inadequacy in diabetic management the present drug regimens have been flagged by various studies, regulatory authorities and clinical observations for several patient safety issues. Sulfonylureas are known to cause Hypoglycemia and, Weight gain and being closely observed for possible increased mortality from cardiovascular disease, and possible increased incidence of cancer.

Metformin is known to cause gastrointestinal symptoms such as abdominal discomfort, diarrhea, anorexia and nausea, lactic acidosis (with impaired renal function) and Vitamin B12 deficiency. Glucosidase inhibitors produce Gastrointestinal discomfort and Borborygmi (stomach growling or rumbling). Thiazolidinediones induces Fluid retention, Edema, Congestive heart failure, Weight gain, Bone fractures, and is being observed for possible increased risk of ischemic heart disease (with rosiglitazone). Dipeptidyl peptidase 4 (DPP-4) inhibitors have been flagged for possible association with acute pancreatitis, possible association with exfoliative dermatitis, and Increased respiratory infections. Insulin produces marked weight gain, severe hypoglycaemia and is being observed for possible increased cancer incidence. Incretin mimetics are known to cause nausea and vomiting and are being observed for possible association with medullary thyroid cancer (liraglutide), and possible association with acute pancreatitis (exenatide and liraglutide)⁵.

Thus the possibility of a new drug overcoming the deficiencies of the present multi-drug regimens is most relevant in the field of diabetes. A new drug of such order might be developed with a wish list of therapeutic activities covering prevention of T2DM, improved glycaemic control, prevention / treatment of macro and micro vascular complications, prevention of intracellular hyperglycaemia-induced increased mitochondrial production of ROS, reduced insulin resistance, arrested decline of β -cell function, possible β -cell regeneration, prevention of weight gain and atherosclerotic changes, improved protection of renal and myocardial cells, compatibility with present drugs and, a prolonged efficacy window. Drugs designed to act against individual molecular targets cannot usually combat multigenic diseases such as cancer, or diseases that affect multiple tissues or cell types such as diabetes and

immuno-inflammatory disorders⁷. Therefore, the possibility of discovering and developing a single molecular entity to address all these therapeutic ends is an extremely rare possibility, probably more dependent on serendipity than logic. Many analysts believe that the current 'one drug fits all' approach may be unsustainable in the future. The growing interest in polypill concept is indicative of the need to collectively address multiple targets, risk factors or symptoms⁸. Combination drugs that impact multiple targets simultaneously are better at controlling complex disease systems, are less prone to drug resistance and are the standard of care in many important therapeutic areas. The combination drugs currently employed are primarily of rational design, but the increased efficacy they provide justifies in vitro discovery efforts for identifying novel multi-target mechanisms. Thus in the management of polygenic syndromes and conditions there is renewed interest in multi-ingredient synergistic formulations⁷.

ROLE OF TRADITIONAL MEDICINE

"There is no alternative medicine. There is only scientifically proven, evidence-based medicine supported by solid data or unproven medicine, for which scientific evidence is lacking" proclaims the editorial of JAMA⁹. "Ayurvedic knowledge and experiential database can provide new functional leads to reduce time, money and toxicity – the three main hurdles in drug development. These records are particularly valuable, since effectively these medicines have been tested for thousands of years on people" concludes Patwardhan et al when discussing Ayurveda as a drug discovery platform¹⁰. Publications of many regulatory bodies, especially World Health Organisation¹¹, and U.S. Food and Drug Administration¹² prescribe approaches for selection of such leads mostly based on subjective evaluation of history of safe use. A multi-criteria decision analysis model described by Neely et al suggests a model objectively analyzing history-of-safe-use and risk of botanicals in an objective, transparent, and transferable system¹³. Since more than a decade, its benefit having been accepted beyond reasonable doubt, much emphasis has been given to this approach of reengineering traditional medicine to suit the regulatory mold of modern drugs. These strong evidence of economic and safety benefits has enticed several pharma companies and governments to take-up this route for discovering new drugs seriously. China is a leader in this respect having more than hundred

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Investigative New Drug applications filed in the US, the largest market for herbal drugs. Indian government recognizing this need and opportunity has recently published the draft amendment in Drugs and Cosmetics Act, and Rules (D&C Act and Rules). This defines phytopharmaceuticals (botanical- based drugs) and defines requirements to evaluate and obtain marketing authorization for such drugs on similar lines to chemical moieties¹⁴.

Bhushan and Mashelkar in a land mark paper published in the Drug Discovery Today, suggest that drug discovery and development need not always be confined to new molecular entities. Rationally designed, carefully standardized, synergistic traditional herbal formulations and botanical drug products with robust scientific evidence can also be alternatives⁸.

Both Traditional Chinese Medicine (TCM) and Ayurveda, over thousands of years have developed various practical theories to create polyherbal formulations in which multiple agents contained in one formula act synergistically¹⁵. A reverse pharmacology approach, inspired by traditional medicine and Ayurveda, can offer a smart strategy for new drug candidates to facilitate discovery process and also for the development of rational synergistic botanical formulations. Ayurvedic texts include hundreds of single or polyherbal formulations as evident from the official "Formulary of Ayurvedic Medicines" published in two volumes by the Department of AYUSH, Government of India. These drugs have been rationally designed and in therapeutic use since many years. Sufficient pharmacoepidemiological evidence, based on actual clinical use, can be generated to support their safety and efficacy. Systematic data mining of the existing formulations' huge database can certainly help the drug discovery processes to identify safe candidates and synergistic formulations. Development of standardized, synergistic, safe and effective traditional herbal formulations with robust scientific evidence can also offer faster and more economical alternatives⁸.

Unorganized Traditional Medicine (TM) or Folk-medicine generally relies on generations of experience which in turn is based on observations and serendipity. Even though, having offered excellent leads for drug discovery, folk-medicines fail to offer a platform to work along with nature in designing new medicines as per the need, mainly

owing to their lack of structured scientific rationality. Even accessibility to a large library of compounds from plants, essential for drug discovery tends to become wasteful, and directionless if the numbers to be screened cannot be reduced on a rational basis. Dr M.S Valiathan in the introduction to his book, Legacy of Charaka, observes that the National Cancer Institute of US randomly screened over 1,80,000 plant extracts from 3500 plant genera during a 20-25 year period without contributing a single drug to the market¹⁶. Science Based Traditional Medical systems (SBTMS) of the world such as Ayurveda and (Traditional Chinese Medicine) TCM offer a structured path to drug development using TM information. Though different, the scientific logic of such systems makes them possible to be used as building blocks for logical design and development. Ayurvedic knowledge helps in designing multi-targeted drugs with combinatorial effects to address symptom complexes presented in diseases such as cancer, cardio-vascular diseases or diabetes.

There are many Ayurvedic drugs available in the Indian market, claiming effective management for many disease conditions. Other than the many traditional drugs mentioned in Ayurvedic text books and referred to by the Ayurvedic formulary of India there are many proprietary formulations available in the Indian market, which are based on novel combinations of ingredients from Ayurveda.

SELECTING THE RIGHT CANDIDATE

It is recognized today that 'discovery- exploration' among Science Based Traditional Medicine (SBTM) should be considered a viable option in developing and delivering botanical drugs with combinatorial effects to address multiple targets in the management of polygenic syndromes and conditions⁸. Even the most stringent among drug regulatory establishments have formulated modified processes for testing and registering such drugs^{12,14}.

There are hundreds of medicines in the SBTM systems, which are mentioned for complex human ailments such as diabetes, arthritis, psoriasis and cancer. Oriental and Occidental SBTM's like TCM, Ayurveda, Siddha, Amchi, Unani and Kampo contains references to many such medicines of natural origin¹⁵. Charaka Samhita, the Ayurvedic treatise devoted to its concepts and practice, (written around 900 BC) and Sushruta Samhita (600 BC) devoted to surgical practices, describes hundreds of

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combinatorial formulae^{17,16}. Ben Cao Gang Mu, a compendium of Medicinal Materials used in TCM, written by Li Shi-Zhen and published in 1587 AD has recorded 1,892 agents and about 11,000 combinatorial formulae¹⁵. Thus, theoretically there are thousands of options to be pursued in SBTM for development into potential botanical drugs.

Regulatory acceptance of such drugs is another major criterion, which is being officially addressed by several drug regulatory bodies through guidelines and directives. Guidelines to Industry on Botanical drugs by US FDA, Traditional Herbal Medicinal Products Directive (THMPD) by European Union, and Phytopharmaceutical drug rule drafted by Government of India are examples of change in mindset by regulatory bodies.

Utilizing SBTMS as resources for designer drugs needs to follow certain parameters. To understand the requirement and utility of the drug requires a holistic view of the disease being addressed. There are several safety assessment approaches for botanicals which enlists criteria to assume safety based on history of use^{13,18,19,20,21,22}. There are many Ayurvedic drugs available in the Indian market, claiming effective management for diabetes. Drug discovery is a process involving humongous cost, effort and time. Any lead followed in this direction needs to be selected with great scrutiny and caution. It is essential to define a set of criteria to assess a traditional poly-herbal drug to be considered as a lead compound in drug development pipeline. These criteria must be designed to assess the safety, probable efficacy and market viability of such drugs.

CONCLUSION

With new insights gained into its pathology and complications, and learning from the deficiencies of currently available therapies, there is scope for developing new drugs for T2DM. These drugs could be multi-ingredient synergistic formulations, that will have multi-targeted effects and manage the polygenic syndromes and conditions presented by T2DM. Science Based Traditional Medical Systems such as Ayurveda offers several formulations, which were in use since centuries and with known safety, to provide multi-targeted benefits for diabetic patients. It is preferable that synergistically formulated traditional drugs with good safety records, be selected as candidates to undergo the

rigorous, time-consuming, costly path of botanical / phytopharmaceutical drug development. A new set of criteria need to be formulated to select the right poly-herbal formulation as a candidate 'lead compound' for drug development. These criteria must be designed to underline the safety, probable efficacy and market viability of such drugs.

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