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New Paradigm for Drug Discovery and Development - Reemergence of Nature's Role

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It is now widely accepted that no single system of medicine is capable of solving all health problems of human race. Collective human wisdom, combined with long and unbroken ethnomedicinal practices, clearly deserves appreciation and understanding of scientific community. Higher plants are capable of synthesizing a fascinating array of highly complex and unusual chemical substances. Their rich structural and stereochemical characteristics make them ideal templates for the development of novel molecular leads for therapeutic purposes. Phytochemicals are thus playing a very important role in global healthcare and economy.

As the developing world faces food security issue, it also confront with drug insecurity. Nation states must prioritise the agenda for developing safe and effective drugs and must act to develop drugs, targeting local diseases. Developing countries need to set up a fund for research and development of drugs to treat neglected tropical diseases like dengue, rabies and tuberculosis (TB). Dr. Panjwani Center for Molecular Medicine and Drug Research, University of Karachi, is an example of an R & D institution, which is engaged in developing remedies for tropical and regional diseases, prevalent mostly in South Asia. We need to focus our attention on poor man's diseases prevalent in the developing countries and to invest in research and development in this sector. Poor man's ailments include a range of diseases caused by individual pathogens and groups of conditions caused by related microbial species. They spread by animal hosts such as dogs, fish or by vectors such as mosquitoes, black flies, snails, bugs and common house flies.

Diabetes mellitus (type-2 diabetes, non-insulin dependent) is the most common form of metabolic disorder. α-Glucosidase inhibitors may be used for the management of type 2 diabetes, as they have the potential to slow down the absorption kinetics of carbohydrates in the small intestine. α-Glucosidase inhibitors themselves do not cause low blood glucose, and can efficiently control the post-prandial hyperglycemia. Based on ethnomedicinal information, we selected several medicinal plants for bioassay-guided phytochemical investigations, which resulted in the identification of a large number of bioactive constituents. These compounds were systematically screened for α-glucosidase inhibitory potential by employing high-throughput mechanism-based bioassay screenings. This has resulted in the identification of novel class of α-glucosidase inhibitors.

Glycation is a non-enzymatic process in which human DNA, lipids and proteins are damaged by the attachment of reducing sugars, which leads to the formation of highly reactive Advanced Glycation Endproducts (AGEs). This process has been associated with deleterious health effects of hyperglycemia and diabetes. An anti-glycation agent that inhibits the glycation process and prevents the formation of AGEs (e.g. free radicals, α-dicarbonyl species, protein cross-links, etc.), therefore has the potential to delay the onset of late diabetic complications. Thus, the goal to develop and identify agents, which can stop or suppress the glycation process but are safe, specific, effective, orally bioavailable and address underlying problem, deserves to be pursued. Based on this need, we screened a large number of medicinal plants, used for the treatment of diabetes in folk medicines. We also screened a

large number of natural and synthetic compounds with novel chemical structures for their antiglycation potential *in vitro* and *in vivo*. As a result, several new classes were identified as potent antiglycating agents.

Multidrug resistance (MDR) is a problem that continues to challenge the healthcare sector. In particular, MDR is now common in familiar pathogens such as vancomycin-resistant *Enterococci* and *Staphylococcus aureus*. This complex problem is related to the degree of exposure to antibiotics, exacerbated by inappropriate use in both developed and developing regions. Our study, focusing on the discovery of natural and synthetic compounds, against MDR bacteria *S. aureus* and *Pseudomonas aeruginosa* (resistant to almost 20 antibiotics) have resulted in the identification of a number of new classes of novel antibiotics.

These studies conducted to build libraries of analogues to study their structure-activity relationship. During this presentation, underlying philosophy and results of these studies will be presented.