SCOPE AND OBJECTIVES OF THE INVESTIGATION

There is increasing awareness in the use of dietary carbohydrates since they promote better health and reduce the risk of various diseases. In this context, the prebiotic non-digestible oligosaccharides (NDOs) have been used as dietary strategies and the majority of research have so far focused on inulin, fructo-oligosaccharides, xylo-oligosaccharides and galacto-oligosaccharides owing to their safety and efficacy. NDOs are food components that confer various health benefits on the host associated with the modulation of the microbiota. NDOs target the indigenous beneficial bacterial community already established in the gut, increasing their proportion to confer positive effects on the gut and other organs through various mechanisms. Moreover, these compounds may prevent pathogen adhesion, enhance barrier function, decrease fecal transit, improve glycemic response and facilitate mineral absorption. Specifically, during pregnancy, NDOs supplementation has beneficial effects on and host metabolism, and may be used to abrogate various pregnancy-related metabolic disturbances.

Number of epidemiological studies have demonstrated that millions of children worldwide are affected with neurodevelopmental disorders. Strong evidence implicates that numerous chemicals disseminated in the environment can cause neurodevelopmental toxicity. The developing ‘brain’ is uniquely vulnerable to chemical exposures at much lower doses and major windows of developmental vulnerability occurs in utero and/or during early postnatal period. Although the placenta offers marginal protection prenatally, the brain continues to develop postnatally and the vulnerability therefore continues through the infancy. During these critical life stages, chemicals can cause permanent injury since the developing brain has lower reserves of protective antioxidants, immature blood-brain barrier, higher neurons to glia, relatively hypoxic environment due to substantially lower oxygen concentration in fetal arterial blood, and more metabolic demand associated with growth thus reducing the safety margin for any chemical agent that compromises oxidative metabolism.
Moreover, persistent industrial compounds accumulate in maternal tissues and are passed on to the infant via breast milk, resulting in higher infant exposures.

Variety of chemicals elicits cellular damage through their shared ability to induce oxidative stress in the neural cells. Oxidative stress and neuroinflammatory processes involving free radical species contribute to the various developmental neurotoxicant profiles (organic substances, pesticides, PCBs and metals). Although developmental exposure to neurotoxic agents results in morphological changes in the CNS, in several cases, the functional changes may be the result of more subtle biochemical/ molecular changes. Such exposures may adversely affect the nervous system associated with co-morbidities: preterm birth, sensory and motor deficits, developmental delays, autism spectrum disorders. It has also been poised that early life events contribute to long term consequences such that developmental neurotoxic insult could also contribute to neurodegenerative diseases, such as Parkinson’s disease (PD).

Recent years have witnessed a rise in literature focused on the impact of enteric microbiota on brain and behavior and, as a result, the concept of the microbiota-brain has emerged. Preclinical literature has shown the bidirectional communication between the brain and the gut microbiota involves multiple mechanisms that are not fully elucidated but includes neural, endocrine and immune pathways. Experimental changes to the gut microbiota have also been shown to affect brain neurochemistry and behavior. From the neurodevelopmental perspective, the microbiota has emerged as a key modulator in neurodevelopmental phases including synaptogenesis, regulation of neurotransmitters and also behaviors relevant to psychiatric pathology. Recent observations suggest that the indigenous microbiota affects developmental programming of the brain both pre- and postnatally. Since vigorous neural development occurs during the perinatal life, it is possible that it can be indirectly influenced by the microbiota of the mother. Hence, the maternal microbiota composition during pregnancy would likely to contribute to the newborn’s brain development. Emerging evidence also points to the relationship
between ‘polyphenols and microbiota’ where the dietary polyphenols modulate the gut ecology. Specifically, the under-utilized agricultural products such as seeds from several plant species often constitute important source of bioactive polyphenols and raffinose oligosaccharides possessing biological potential.

Two experimental neurotoxin models employed in the present investigation are a) Acrylamide, a well-known food contaminant/ neurotoxin and b) Rotenone, a pesticide and well-established DA toxin. The neurodegenerative process induced by both the chemicals involves elevated levels of oxidative and pro-inflammatory factors. Given the possible neurotoxic effects associated with the exposure to developmental neurotoxicants beginning in utero, it is relevant to develop specific dietary strategies aimed at modulating gut ecosystem and consequently mitigates neurotoxicity. It is quite likely that understanding the connection between modulatory role of NDOs on gut flora and brain will open new avenues for improving the therapeutic potential for specific CNS disorders.

Accordingly, this proposal aims to assess the potential of selected NDOs during pregnancy to alleviate developmental neurotoxicity pre- and postnatally in rodent model. The second focus of the thesis was to investigate the utilization of Drosophila model to assess the efficacy of NDOs and NDO-enriched phytochemical extract to alleviate oxidative stress-mediated neurotoxicity. The hypothesis of this investigation is based on the premise that NDOs owing to their antioxidant property and ability to modulate microbiota may possess propensity to protect the brain against developmental neurotoxicity.

Objectives
- To examine the protective role of non-digestible saccharides against selected developmental neurotoxicants in Drosophila and rodent model.
- To obtain insights on the involvement of oxidative stress and inflammatory mechanisms following exposure to developmental neurotoxicants during gestation period (prenatal) and postnatal period in rodents.
- To establish the role of altered microbiota on the neurotoxicant-induced biochemical/ molecular perturbations and its impact on brain development and behavioral functions in rodents.