Pharmacological chaperones (PCs) are a promising strategy for the treatment of genetic disorders based on enzyme enhancement therapy, such as phenylketonuria (PKU). PKU is a common in-born error of amino acid metabolism that is related to more than 500 disease-causing mutations of phenylalanine hydroxylase (PAH) or by a defect in the synthesis or regeneration of tetrahydrobiopterin (BH4). To date, lifelong dietary Phe-restriction and BH4 supplementation are the only accepted treatment options for PKU patients. However, special low-protein diets can lead to malnutrition, psychosocial or neurocognitive complications due to poor compliance, while BH4 therapy is costly and only 20-30% of PKU patients are responsive.

Using a novel screening strategy to identify small molecules from a chemical library with chaperone activity, McMaster researchers have identified plant-derived natural products (and synthetic analogs) that enhance the activity of denatured/inactive wild-type PAH and two clinically relevant PKU mutant enzymes. These plant-derived natural products are present in variable amounts in the human diet and thus offer a safe yet effective therapeutic treatment of PKU via nutritional supplementation, notably for patients with severe phenotypes.

Applications and Advantages
- Enzyme replacement therapy has recently been shown to reduce plasma Phe levels by 40% in mouse models of PKU. However recombinant enzyme therapy is costly and requires careful monitoring to avoid toxicity and immunogenicity.
- Only a handful of studies have identified putative PCs to correct the folding of PKU mutants and most of these have had only modest efficacy in enhancing mutant PAH activity.
- The current PCs can be administered orally and are safe natural products already present in the human diet. They offer a simple way to rescue mutant PAH from cellular degradation in vivo thus enabling rapid clinical translation. An unprecedented 5-fold enhancement in mutant PAH activity has been demonstrated with lead PC candidates.