Demystifying Chronic Kidney Disease of Unknown Etiology (CKDu): Computational Interaction Analysis of Pesticides and Metabolites with Vital Renal Enzymes

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Abstract: Chronic kidney disease of unknown etiology (CKDu) has been recognized as a global non-communicable health issue. There are many proposed risk factors for CKDu and the exact reason is yet to be discovered. Understanding the inhibition or manipulation of vital renal enzymes by pesticides can play a key role in understanding the link between CKDu and pesticides. Even though it is very important to take metabolites into account when investigating the relationship between CKDu and pesticides, there is a lack of insight regarding the effects of pesticide metabolites towards CKDu. In this study, a computational approach was used to study the effects of pesticide metabolites on CKDu. Further, interactions of selected pesticides and their metabolites with renal enzymes were studied using molecular docking and molecular dynamics simulation studies. It was evident that some pesticides and metabolites have affinity to bind at the active site or at regulatory sites of considered renal enzymes. Another important discovery was the potential of some metabolites to have higher binding interactions with considered renal enzymes compared to the parent pesticides. These findings raise the question of whether pesticide metabolites may be a main risk factor towards CKDu.

Keywords: CKDu; renal enzymes; pesticides; metabolites; molecular docking; molecular dynamics

1. Introduction

Chronic kidney disease (CKD) is a global health and economic issue. It is characterized by a gradual decrement of glomerular filtration rate (GFR) over time due to structural and functional defects of kidney in urinalysis, biopsy, and imaging [1]. The leading causes for CKD are thought to be glomerulonephritis, hypertension, and diabetes mellitus [2]. CKDu is an evolving health problem in some low and middle-income nations, such as El Salvador, Egypt, Cuba, Sri Lanka, Bangladesh, and India [3]. The poor rural areas are most affected with agricultural work being the dominant occupation. Poverty with the absence of access to health care makes it hard to determine the clinical features of CKDu. In Nicaragua, Central America, the highest prevalence of CKDu has been reported with 10–20% cases among the adult population [4], where the third to fifth decade age group is highly affected. In Southern India and Sri Lanka, CKDu prevalence is 1.6 and 1.5%, respectively (ref), where a wide age range is affected. Generally, the male prevalence is significantly higher than in females [5,6].

Progression of CKDu is usually symptomless until advanced phases of the disease, in which the kidneys are irreversibly damaged, resulting in mortality unless dialysis or transplantation occurs [7]. The CKDu endemic in Central America is called Mesoamerica Nephropathy (MeN). The patients have elevated serum creatinine levels and normal albuminuria [8]. Podocytic changes, Glomerulosclerosis and moderate tubulointerstitial damages were observed in MeN patient kidneys [9]. This suggests that the added stress