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REVIEW OF LITERATURE ON THE ROLE OF NATURAL MEDICINAL SUBSTANCES IN KIDNEY DISEASES BY MANAGING CREATININE URIC ACID AND OTHER BIOMARKERS

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Abstract: The current unidimensional paradigm of kidney disease detection is incompatible with the complexity and heterogeneity of renal pathology. The diagnosis of kidney disease has largely focused on glomerular filtration, while assessment of kidney tubular health has notably been absent. Following insult, the kidney tubular cells undergo a cascade of cellular responses that result in the production and accumulation of low-molecular-weight proteins in the urine and systemic circulation. Modern advancements in molecular analysis and proteomics have allowed the identification and quantification of these proteins as biomarkers for assessing and characterizing kidney diseases. In this review, we highlight promising biomarkers of kidney tubular health that have strong underpinnings in the pathophysiology of kidney disease. These biomarkers have been applied to various specific clinical settings from the spectrum of acute to chronic kidney diseases, demonstrating the potential to improve patient care.
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Introduction:

Kidney diseases are complex and heterogeneous. Yet, clinical assessment of kidney disease largely relies largely on the glomerulus, the specialized filtering unit of the kidney. This unidimensional paradigm limits diagnosis and treatment of kidney diseases, the consequences of which are readily apparent: Both acute and chronic kidney diseases continue to outpace clinical management and are increasingly recognized as significant global health problems. And because these conditions are detected too late in the disease course, there have been no effective treatments developed to minimize kidney injury, alter the course of disease, or limit the associated morbidity and mortality.

Specifically, the diagnosis of kidney disease has relied on the serum creatinine, a breakdown product of creatine and phosphocreatine, that is largely freely filtered by the glomerulus. Accessible and affordable, serum creatinine has remained the gold standard for almost a century, despite its many well-recognized limitations as an indirect marker of kidney damage, including delayed detection of injury. In addition, serum creatinine can increase in the absence of glomerular or tubular injury and can be unchanged under conditions of significant tubular injury, particularly when patients have good underlying kidney function and significant kidney reserve current biomolecular identification techniques expose new aspects in the biological universe of the human body (1). Omics strategies through genomics, metabolomics, lipidomics and proteomics generate thousands of information that demand math resources to integrate and translate the meanings of multiple molecular patterns in the construction of modern biochemical knowledge of the interior environment.

The molecular scenarios designed with these tools contain biomarkers that, together or in isolation, are potentially capable of predicting or confirming diagnoses, guiding therapeutic strategies and predicting clinical outcomes. Biomarkers are endogenous molecules, detected qualitatively and/or quantitatively, which provide peculiar data for the identification of physiological or pathophysiological processes, as well as for the control of pharmacological responses. After more than a century restricted to the first biomarkers for the detection of kidney dysfunction—urea and creatinine (Cr), and

kidney damage—proteinuria, nephrology now has a series of new molecular information and submits them to repeated validation so that they can be properly incorporated into clinical practice (2).

Kidney biomarkers can be classified according to the morphophysiological characteristics of the nephron, related both to the renal function (glomerular and tubular) and to the integrity of its endothelial or epithelial cells The development of these biomarkers is not focused on the identification of a specific disease, but on the detection of a renal pathophysiological phenomenon, with variable complexities and etiologies. The absence or normal levels of certain biomarkers can also be clinically useful to define negative predictive values for various pathologies.

Review of literature:

Chronic kidney disease (CKD) is one of the leading causes of death globally, which affects 13.4% of the world's population [1]. With deterioration in renal function, this leads to the onset of CKD-related complications, such as uremia, anemia, and electrolyte disorders [2]. These complications often manifest as symptoms ranging from pruritus, pain, and insomnia to muscle cramps. This in turn has negative implications on patients' quality of life [3,4]. Importantly as CKD patients approach end-stage renal disease (ESRD), the prevalence and severity of such symptoms increase [5].

Despite medical breakthroughs and the advent of new therapies in the past decades, optimal treatments for some of the symptoms resulting from CKD-related complications remained unclear, possibly due to their complex pathophysiology. A case in point is uremic pruritus, which is found in around 20% of pre-dialysis CKD patients and 40% of ESRD patients [6]. Although prevalent treatments include the use of emollients, gabapentin, and antihistamines, data related to their efficacy were often derived from small studies and their use is limited by adverse effects [7].

The use of alternative medical systems (AMS) which forms a key pillar of complementary and alternative medicine (CAM) has increased in the past 20 years [8]. AMS is defined as "entire systems of health theory and practice that developed separately from conventional medicine" [9]. Notably, around 18% of dialysis patients have utilized some form of AMS [10,11]. In addition, prescription of AMS therapies such as traditional Chinese medicine (TCM) by professional practitioners often aids in minimizing the risk of side effects, hence increasing their appeal as potential therapeutic alternatives [11].

Prior studies have shown that AMS is effective in reducing symptoms such as pain, nausea, and fatigue in non-CKD patient populations. For instance the use of TCM formulas, such as Liu Junzi Tang and Xiao Banxia Plus Fuling have demonstrated efficacy in treating cancer-related pain and chemotherapy-related nausea and vomiting [12]. In addition, Chinese herbs such as *Curcuma longa* and *Panax ginseng* among patients with malignancies have shown efficacy in promoting apoptosis of cancer cells and inhibiting tumor metastasis [13]. Another study showed that a multi-modal Ayurvedic treatment approach was effective in reducing knee osteoarthritis symptoms, such as pain and stiffness, and improving function [14]. With increasing research supporting the use of AMS, this has led to a rise in healthcare institutions adopting and providing such integrated services which are supported by insurance coverage [14].

Among CKD patients, multiple studies have also been conducted to assess the efficacy of AMS in the treatment of CKD-related conditions and symptoms such as uremic pruritis and anemia. For instance, a study that assessed the efficacy of homeopathy verum among CKD patients showed a reduction in pruritus symptoms by 49% after 30 days of treatment [8]. Another study that evaluated the use of TCM patients with glomerulonephritis showed improvement in hemoglobin after 24 weeks of therapy [9].

Existing reviews which have assessed the role of AMS are currently limited to specific indications, such as uremic pruritus [8], use of subtypes of AMS in specific CKD subgroups, such as consumption of Chinese herbal medicine in diabetic kidney disease [9], and specific AMS therapies, such as use of Astragalus [14]. This review aimed to summarize and evaluate the broad roles and efficacy of AMS as potential alternative therapeutic options for CKD patients. Findings from the review will aid physicians in gaining a better understanding of the efficacy of AMS for CKD patients, which can aid in facilitating purposeful discussions with patients who are using or considering these therapies.

The important role of kidneys in normal physiology comprises plasma filtration of metabolic waste products, regulation of plasma volume, hormone secretion and acid-base balance. Any changes in the above indicators lead to a large number of diverse, life

threatening renal diseases. Globally, the 12th cause of death in humans is due to chronic kidney disease (CKD) and leads to 17th cause of disability. People with CKD are more prone to cardiovascular disorders (CVD) rather than to reach end-stage renal disease (ESRD) [1]. Around 30% of diabetes mellitus patients (DM) fall ill with diabetic nephropathy (DN) and CKD incidence. According to the Diabetes Atlas 2006 (India), patient's population with DM is presumed to rise to 69.9 million by 2025 in the absence of preventive measures [2]. "Screening and Early Evaluation of Kidney Disease" (SEEK), a voluntary health screening program which is community-based started in 2006 in India performed analysis of urine and serum creatinine of people. SEEK announced high prevalence of CKD approximately 17.4% applying a glomerular filtration (eGFR) formula. Indian CKD Registry states that diabetes (all types) is the cause of kidney disease in 30% of the patients enlisted in their studies. Just 20% of the ESRD registered patients are on some renal replacement therapies (RRT) [3] . The limitation of ESRD is that it is inpatient thus hospital-based and not an exact figure of population suffering from ESRD. The yearly incidences of ESRD in India is approximately 150–200 per million population (pmp) and Diabetes mellitus is an essential cause of CKD in around 30–40% of these patients [4]. It is evaluated that only 10–20% patients in India with ESRD carry out long-term RRT. In India 3,500 new kidney transplant take place annually, about 3,000 new continuous ambulatory peritoneal dialysis (CAPD) gets initiated and 15,000 new maintenance hemodialysis (MHD) patients [5]

Urine microalbuminuria, especially in patients with DM, is a first indicator in patients at risk of kidney disease well ahead the rise in gross proteinuria or elevated serum creatinine. Deviation in the level of GFR measured from serum creatinine indicates any kidney disease at an early stage [6]. Diabetic nephropathy can be explained with change in levels of microalbuminuria, succeeded by macroproteinuria and also reduction in GFR. Moreover, renal disease in DM can happen without excretion of protein in urine of patients with DM and kidney disorders [7] . Plasma filtration and most of tubular reabsorption occurs in renal cortex, an important functional portion of the kidney present in between the renal capsule and renal medulla, comprising of glomeruli, proximal and distal tubules. Among all studies renal pathologies, diabetic nephropathy (DN) is predominantly most common causes of renal insufficiency culminating in renal failure. DN is a generally a glomerular disorder but recent scientific literature have focused on the marked changes in tubulointerstitial parameters which strongly suggest that approaches concentrating only on either glomeruli or tubules are not sufficient for thorough knowledge of the pathophysiology of complicated renal diseases such as DN [8].

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