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The Potential of Propolis in Chronic Kidney Disease with Bone and Mineral Disorder: A Literature Review

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ABSTRACT

Chronic kidney disease (CKD) is a heterogeneous syndrome characterized by a decline in glomerular filtration rate (GFR), an increase in serum creatinine within less than 7 days, and/or the presence of oliguria. Chronic kidney disease occurs progressively, evidenced by structural changes and a decline in kidney function for more than 3 months. The causes of chronic kidney disease are diverse, but there are two main pathophysiology underlying CKD: prolonged inflammation and oxidative stress. CKD-MBD (Chronic Kidney Disease-Mineral and Bone Disorder) is one of the common complications that often occurs in CKD patients. It results from a disruption in the homeostasis of phosphate and calcium, leading to excessive resorption of bone matrix and potentially causing complications such as osteoporosis and vascular calcification. Propolis is a bee product with anti-inflammatory and antioxidant effects. Propolis has been proven effective as an adjunctive therapy for patients with chronic kidney disease. Additionally, propolis has protective effects on bones in various diseases, such as osteoporosis and fractures. However, to date, no studies have demonstrated the effects of propolis on bone in chronic kidney disease models.

Keywords: chronic kidney disease; bone; osteoblast; osteoclast; propolis.

INTRODUCTION

Chronic kidney disease (CKD) has been one of the biggest global burdens with a prevalence of at least 10% and causes 1-2 deaths every year.[1] According to prediction this number will continue to increase and will be the number 5 most common cause of death in the world.[2] CKD is a progressive disease shown by structural alteration and decline in function.[3] In the early stage there are almost no symptoms could be observed. Although CKD is caused by many factors two main pathways have been observed as the main pathologies that are prolonged inflammation and oxidative stress.[4]

CKD is highly associated with many complications such as hypertension, anaemia, metabolic acidosis, hyperkalemia, and bone and mineral disorder[5]. Bone and mineral disorders are the most common complication in CKD usually called Chronic Kidney Disease Bone and Mineral Disorder (CKD-MBD) is a systemic syndrome caused by CKD due to the disruption of calcium and phosphate balance in the body[6]. It happens through the disruption of the bone, kidney, gut, and parathyroid hormone axis.[7] Factors such as reduced vitamin D, and hypocalcaemia, will lead to increased secretion of PTH and induced secondary hyperparathyroidism.[6] This condition will also disrupt bone mineralization where calcium will be reabsorbed from skeletal tissue to systemic circulation tissue.[7]

Currently, the treatment for CKD is very limited, that are dialysis and renal transplants.[8] Dialysis is a strategy to replace renal function from filtration, resorption, and also secretion.[8] One of the most common types of dialysis is hemodialysis[9]. It is not as effective as renal transplant its function only replacing renal function and not treating the main cause of CKD, is it also highly costly. Even more, haemodialysis comes with many complications such as fractures. The 1-year mortality rate for haemodialysis is also quite high approximately 25% of haemodialysis died just 1 year after the treatment[10].

Propolis is a bee product that has been widely used in traditional medicine, especially in infectious diseases.[11] This is highly possible due to its anti-inflammatory and anti-oxidant properties. Propolis contains a lot of bioactive components such as flavonoid and phenolic acid.[12] Many animal and clinical studies show the potential of propolis in many chronic diseases such as diabetes, dyslipidemia, cardiovascular disease, chronic inflammation, and also CKD[13]. Although there is no study specifically on CKD-MBD the use of propolis also shows a promising result in bone health such as in osteoporosis, fracture healing, and many more.[14]

REVIEW CONTENT

1. Kidney Disease

1.1 *Chronic Kidney Disease*

Chronic kidney disease is a clinical syndrome secondary to irreversible, slow, and gradual changes in the structure and function of the kidneys. Someone is diagnosed with CKD when there is a reduction of glomerular filtration rate (GFR) under 60 ml/min/1.73 m2 with structural pathology for at least 3 months or more. The causes of CKD vary from hypertension, diabetes, HIV, Hepatitis C, Malignancy, autoimmune disease, nephrolithiasis, and many more[15]. According to KDIGO 2012, CKD could be classified into stages using albuminuria and proteinuria[16].

Chronic kidney disease comes from unresolved acute kidney injury, starting from prolonged inflammation, microvascular disruption, and abnormal remodeling will lead to the decline of renal function gradually and permanently that usually called maladaptive repairment. This is due to tubular epithelial cell destruction, endothelial disruption and capillary density, inflammation, and interstitial fibrosis.[16]

Epithelial cells especially in the tubular are the most prone to destruction and become the most common cause of acute kidney injury (AKI). In normal conditions, epithelial cells could actively regenerate from many disruptions such as ischemia, obstruction, and toxin. During this pathological state, most of the epithelial cells have become stagnant at the G2/M phase[16]. At this phase, epithelial cells would release pro-inflammatory cytokines such as proinflammatory, profibrotic, and transcriptional growth factors such as TGF-β, PDGF, CTGF, and VEGF[16,17].

The death of epithelial cells also releases pro-inflammatory and damage-associated molecular patterns (DAMPs) that will activate innate immunity[17]. This will lead to further inflammation by activating innate and adaptive immunity activating myofibroblasts that lead to fibrosis[18]. Interestingly in CKD macrophage has 2 functions in the first phase macrophage will be polarised and turn into pro-inflammatory M1 that produces pro-inflammatory cytokines such as TNF-α and IL-6[19]. In the second phase, this macrophage will turn into the M2 counterpart which possesses anti-inflammatory properties by producing IL-0 and TGFβ1 that help with regeneration and remodelling phase[20]. This also happened to T cells in the early stages the number of T cells rapidly increased in the renal lymphatic system and migrated to the renal tissue releasing pro-inflammatory cytokines such as INFɣ that activate macrophages[21]. While in the regeneration state T cells regulator suppresses inflammation by releasing IL-10[22].

1.2 CKD-MBD

CKD-MBD is a condition where mineral and bone metabolism are disrupted in CKD patients. It happened early on in the disease but only showed symptoms when hyperphosphatemia, hypocalcemia, and hyperparathyroidism happened. This is due to the ability of the renal to adapt when the number of nephrons decreases the remaining nephron will increase its filtration function to maintain homeostasis[7]. The decrease of nephrons will lead to an increase in phosphate retention causing hyperphosphatemia, reduced vitamin D, and hypocalcemia that could lead to secondary hyperparathyroidism. In contrast, the serum phosphate level will increase only when the disease has reached late stages due to the role of Fibroblast Growth Factor-23 (FGF-23) and Parathyroid hormone (PTH)[6,7].

FGF-23 and PTH are the main hormones controlling phosphate homeostasis in our body. FGF-23 has a beneficial effect in the short term but in the long run, could cause complications[23]. The level of FGF-23 decreases and the GFR falls in CKD and is highly connected to secondary hyperparathyroidism in CKD. In the early stage of CKD FGF-23 will reduce the level of phosphate retaining phosphate level in the body. However, in the later stages of CKD, it will also suppress Vitamin D and PTH. The reduction of PTH level will induce the parathyroid gland to proliferate causing hyperplasia and ending with secondary hyperparathyroidism[24].

Renal osteodystrophy is a clinical condition picturing many bone abnormalities in CKD patients[7]. This happened due to dysregulation of the bone renal-bone-gut axis with parathyroid glands[25]. Bone remodeling in CKD mainly happens through two mechanisms. The first mechanism is due to reduced vitamin D synthase and vitamin D (VDR) gene expression in osteoblast this will reduce bone mineralization[26]. Another mechanism is through the dysregulation of PTH. Although PTH induces osteoblast proliferation there is a reduction in osteoblast function due to the lack of Runx2 protein[27]. This increased proliferation of osteoblasts is also followed by osteoclast proliferation. Hyperparathyroidism accompanied by hyperphosphatemia and reduced vitamin D will promote the mobilization of calcium from bone to systemic circulation[27,28].

2. Propolis

2.1 *Definition, Pharmacology Properties of Propolis*

Propolis is a material used by bees as a honeycomb protection system derived from various kinds of plant sap to protect the hive from various predators and maintain the condition in the hive[29]. Propolis has long been used in Chinese traditional medicine to fight against infectious disease[29]. It contains there are around 500 bioactive components mainly flavonoid and polyphenol[30,31]. According to Šuran et al. (2021), polyphenols are chemical compounds that have aromatic rings and one or more hydrogenated substituents to their functional derivatives[31]. Flavonoids, such as flavonoid chrysin, flavonol galanin, and flavonoid pinocembrin, are often the polyphenol components found in propolis. Furthermore, phenolic acids are classified according to their derivatives, specifically from benzoic acids like gallic acid and protocatechuic acid and from

cinnamic acids such as caffeic, and ferulic acid, in addition to flavonoids [32].

Propolis's composition with rich molecules like oil, wax, and rubber results in a relatively poor bioavailability. The bioavailability of propolis is further influenced by stability, diffusion capacity, metabolism rate, and excretion. Furthermore, permeable membrane selection and systematic elimination also affect the effects of propolis in blood[33]. Some research indicates that rats' blood-brain barrier can be crossed by caffeic acid phenethyl ester (CAPE)[34]. This is due to the fact that CAPE undergoes hydrolysis and becomes caffeic acid after six jams[13]. Individual differences exist in the effects of polyphenol in urine, which are strongly linked to aging, renal function, and the characteristics of propolis itself[35].

2.1 *Anti-inflammation Properties of Propolis*

Many studies have proven that propolis has a strong anti-inflammatory effect on both acute and chronic inflammation[36]. This is due to the active content of flavonoids and phenolic acids of the cinnamic acid group, such as acetin, quercetin, naringenin, CAPE, and CA[37]. The main mechanism is the suppression of pro-inflammatory cytokines such as TNF-α and IL-1β; increases in anti-inflammatory cytokines such as IL-4 and IL-10; TLR4 activation inhibition; expression suppression of LOX, COX-1, and COX-2; suppression of NF-κB and AP-1 activities; and reduction from monocyte and neutrophil infiltration[38].

Flavonoids inhibit NF-κB, which has an important role in the induction of various pro-inflammatory genes that induce the release of cytokines, chemokines, and inflammasomes, especially in the activation and differentiation of T cells[37]. This inhibition occurs due to the activation of anti-inflammatory pathways such as Sirtuin-1 (Sirt1), which will interfere with TLR4/NF-κB/STAT signals, resulting in a decrease in the production of anti-inflammatory cytokines and chemokines[39].

The flavonoid content in propolis can inhibit the expression of LOX, COX-1, and COX-2. This will lower the levels of various mediators such as leukotriene (LTC4, LTD4, LTB4), thromboxane A2 (TXA2), prostaglandins (PGE2, PGG2, PGF2, PGI2), and Cisteinil[37]. Inhibition is caused by the derivation of c-Jun-N-terminal kinase (JNK1/2) and NF-κB inhibition so that COX-2 expression will decrease[40]. COX-2 is a pro-inflammatory enzyme that plays an important role in recruiting immune cells so that there is a decrease in monocyte and neutrophil infiltration[37].

Flavonoids also inhibit the release of histamine by mast cells and basophils. This is done in 2 ways, namely the inhibition of the cAMP phosphodiesterase enzyme, which will increase histamine production. As well as inhibition of calcium influx through calcium-dependent ATPase inhibition[37]. In addition, flavonoids have a high affinity for mast cells and basophils, which will stabilize the membrane and prevent degranulation from occurring[41]. This inhibition of mast cell degranulation will also decrease pro-inflammatory cytokines such as TGF-β, IL-4, and TNF-α so that fibroblast activation and proliferation do not occur[37].

2.3 *Propolis and CKD*

Propolis has been widely used in various studies on chronic kidney failure, ranging from animal to human trials, as adjuvant therapy[13]. At a dose of 500 mg/day for 12 months in patients with chronic renal failure, there was a decrease in the inflammatory marker monocyte chemoattractant protein-1 (MCP-1) in the urine[42]. Another study showed that at a dose of 1000 mg/day for 90 years in patients with chronic kidney failure with type 2 diabetes mellitus, there was a decrease in inflammatory markers of high-sensitivity C-reactive protein (hs-CRP) and TNF-α as well as interleukin-1β (IL-1β) and IL-6 but not significantly[43]. In addition, supplementation of 500 mg/day in patients with chronic kidney failure significantly decreases proteinuria. Propolis also showed systemic positive effects, such as a decrease in BP in patients with renal failure with hypertension and an improvement in lipid profile with an increase in HDL-C levels[42].

2.4 *Propolis and Bone Disorder*

Propolis has effects on both osteoblasts and osteoclasts[44]. Propolis decreases activation and differentiation of osteoclast-like cells (TRAP) from macrophages and bone marrow cells. Bone marrow cells. In addition, propolis also reduces TRAP-positive cells from human peripheral blood mononuclear cells (hPBMCs). This is done through decreased activation of expression of osteoclast-specific genes such as receptor activator of nuclear factor kappa B (RANK), nuclear factor of activated T cells 2 (NFAT2), cathepsin K, chloride channel 7 (CLCN7), and calcitonin. calcitonin, calcitonin receptor (CTR)[45].

Propolis also increases the activity and differentiation of osteoblasts. Propolis increases mineralization and ALP activity in the osteoblast-like MG-63 cell line in humans. In addition, the expression of osteoblast differentiation genes such as runt-related transcription factor 2 (RUNX2), osterix (OSX), osteocalcin, and type 1 collagen alpha also increased[46]. In addition, propolis also reduces parathyroid hormone. (PTH) and calcitonin levels in rats. The effects of These bone homeostasis effects of propolis have a high potential in preventing osteoporosis. osteoporosis[44]. Administration of propolis at a dose of 200 mg/kg/day for 3 weeks showed an increase in bone mineral density, radiologic tail, and histology. Density, radiologic tail, and histology in rats with fractures and retrograde fixation [47]. Propolis also increases the ability of bones to withstand stress in the ulnar radius complex in rats with non-union bone disorder[48].

CONCLUSION

Chronic kidney disease has been one of the biggest challenges we are facing in the medical world with many complications, including bone and mineral disorder, becoming the most common complication

among CKD patients. Propolis is one of many bee products. It offers great benefits for chronic diseases such as CKD. Although currently there are no studies that analyze the benefit of the use of propolis in patients with chronic kidney disease with bone and mineral disorder, it might promise a great benefit. Propolis has an anti-inflammatory effect that has been speculated to be one of the main pathophysiologies of CKD. Even more, propolis also has a great benefit on bone health itself; it has been proven in many animal and clinical studies. Further studies on animal and human models are needed to observe the efficacy and optimal dose of propolis in CKD-MBD.

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