**Original Article**
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# The Effects of Curcumin on Olfactory Dysfunction and Indoxyl Sulphate in Hemodialysis Patients

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***Abstract***

***Introduction:***
Neurological abnormalities in uremic conditions are indicated by olfactory impairment in the population with long-term renal disease, which escalates in prevalence with the degree of severity of renal disease. Indoxyl Sulphate is a kind of toxic substance that exacerbates kidney damage. Since it scavenges ROS or reactive oxygen species, curcumin helps prevent disease development and promotes olfactory ensheathing cell growth and viability under normal and hypoxic settings.

***Materials and Methods:***
For 12 weeks, 48 patients with stage 5 chronic renal disease receiving regular haemodialysis were split into three groups: the control group, the 500 mg curcumin group, and the 1000 mg curcumin group. Plasma indoxyl Sulphate concentrations and subsequent olfactory function were assessed. The results were compared using bivariate and multivariate analysis.

***Results:***
The olfactory function delta (p=0.002) and discrimination of olfactory delta (p=0.001) of the 500 mg and 1000 mg curcumin groups differed significantly. The 500 mg curcumin group's IS levels (p=0.008) and the control group's (p=0.019) delta IS level (p=0.870) were significantly different from the 1000 mg curcumin olfactory group's olfactory identification (p=0.006) and delta identification (p=0.618). The olfactory thresholds of the three study groups did not differ significantly (p=0.636).

***Conclusion:***
Curcumin therapy alleviated olfactory impairment in individuals with chronic renal illness; no increase in indoxyl Sulphate levels was observed, suggesting that curcumin may stabilize the toxin.

***Keywords:*** Curcumin, Indoxyl sulphate, Olfactory dysfunction, Chronic kidney disease

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## Introduction

Patients with chronic kidney disease (CKD) are increasingly acknowledged to have olfactory impairment as a serious issue. It can result in a number of problems, including as malnutrition and food aversion, which are serious problems for this group. Research has indicated that people with chronic kidney disease frequently experience olfactory impairment, with varying severity depending on the stage of the disease (1). Seventeen studies met the criteria from a review of 832 articles, which provided an overview of olfactory impairment in 4,025 CKD patients. The statistics demonstrated that 55.34% of the population analysed exhibited olfactory impairment, whereas 8.5% were diagnosed with anosmia (1). Potential reasons for impairments of olfactory in people with chronic kidney disease (CKD) include diminished capacity and compromised cells regeneration of epithelium from olfactory system due to uremic toxins. Impairment of olfactory may indicate neurological impairment in the population with long-term renal disease and offer new perspectives on uremia. Uremia may impact peripherally located olfactory neuroepithelium and greater central processing pathways (2).

Indoxyl Sulphate (IS) is a protein-bound toxin recognised as a risk precursor to disease development in the population with long-term renal disease, accumulating when the renal tubule excretory function is compromised. Conversely, in healthy individuals, its levels approximate zero (3). Elevated oxidative stress correlates with a disparity between reactive oxygen species (ROS) generation and their breakdown (4). Oxidative stress may be induced by elevated prooxidants and/or diminished antioxidants (5). Indoxyl sulphate stimulates the production of reactive oxygen species (ROS) in several cell types by lowering glutathione levels and activating NADPH oxidase (6). A study including CKD patients undergoing haemodialysis and experiencing olfactory abnormalities revealed a correlation between alterations in smell test results and clinical nutritional indicators. No correlation was identified between levels of uremic toxins, including, P-cresol sulphate, ethylamine, Monomethylamine, and indoxyl sulphate (7). Curcumin significantly contributes to disease prevention by modulating biological processes. It effectively scavenges reactive oxygen species (ROS), which prevents disease pathogenesis (8), another study, antioxidant activity was achieved by inhibiting the regulated onset of styrene oxidation (8).

Investigations concerning the impact of curcumin on impaired smell and Indoxyl Sulphate concentrations in patients with long-term renal disease remain notably scarce. This research evaluates the efficacy of curcumin in improving olfactory disorders based on indoxyl Sulphate levels and olfactory examination in CKD patients. Based on the description above, we hypothesize that curcumin is a potential and effective herb to improve olfactory disorders in CKD patients on regular hemodialysis through Indoxyl Sulphate (IS) levels and Sniffin' Stick Test results.

## Materials and Methods

This research employs an experimental design utilising a Randomised Control Trial (RCT) methodology because this design is to ascertain the impact of intervention or intervention on the given sample. In this study, a total of 48 participants were selected as for random sampling according to the criteria, then for random allocation they were assigned in three groups (16 participants in each group), We prepared 48 cards with three different color categories: 16 red cards for the control group, 16 yellow cards for the 500 mg treatment group, and 16 green cards for the 1000 mg treatment group. We placed the 48 cards in a closed box. Participants were instructed to pick one card from the box, so they didn't know which color they were picking. Each participant was allocated to be either the control group or one of the two treatment groups.

Consecutive sampling serves as a method for sample selection. All participants who fulfil selecting criteria are incorporated into the analysis until the requisite sample size is achieved. Although consecutive sampling was used for feasibility, sampling bias could have been minimized through random allocation after random sampling in this study, thereby improving the generalizability of the findings. Through randomisation, researchers provide each participant with an equal opportunity for group assignment, so ensuring comparability on

dependent factors by mitigating potential bias. This study was performed at the haemodialysis unit of Adam Malik Hospital to assess olfactory function through the use of the Sniffin' Stick test.

**Sample**

The participants in this study were patients with stage V chronic kidney disease (CKD) undergoing regular haemodialysis. The CKD diagnosis was confirmed by a Nephrology Consultant ,an Internist. Participants were aged between 16 and 55 years, received haemodialysis twice weekly, had a history of renal illness varying from under 5 years to over 5 years, and exhibited normal results from routine ENT examinations. Patients with abnormal ENT physical tests were excluded from this investigation, including infections, congestion, persistent rhinitis, pulmonary asthma, infections of the upper respiratory tract, and recent Recent head trauma during the preceding fourteen days, a patient exhibiting uncooperativeness throughout the assessment, inadequate general condition, and a patient who opted out of the research. The sample size comprised 48 patients divided into three groups based on the dose of curcumin: control group or placebo, 500 mg curcumin, and 1000 mg curcumin. 16 patients for each group who had met the inclusion criteria.

**Procedure**

Before the research is carried out, to ensure that all procedures are ethical, the project must initially be presented to the Ethics for Research Council of the University of North Sumatra to secure an evaluation and approval of ethical viability, identified by the number 187/ KEP/ USU/2024.

Blood samples, approximately 3 mL, were collected soon before to the patient's haemodialysis and analysed for indoxyl Sulphate (IS) levels in tubes containing EDTA. The specimen of blood was maintained at room temperature for two hours or at 2°C – 8°C overnight prior to centrifugation for 20 minutes at 3000 rpm. The supernatant was collected as a sample prepared for analysis. Plasma indoxyl sulphate levels can be assessed immediately, or the prepared sample may be preserved in an aliquot at -20°C or -80°C until analysis is conducted at the Comprehensive Research Lab of the Medical Faculty, University of North Sumatra. The evaluation of oflactory ability was performed using the Sniffin' Stick Test (Burghart, Holm, Germany), which evaluates all aspects of olfactory capability: Threshold, Discrimination, and Identification. Subjects were administered curcumin capsules orally at dosages of 500 mg/day and 1000 mg/day for a duration of 12 weeks. The curcumin employed is an extract from turmeric (Curcuma longa), standardised through HPLC (High-Performance Liquid Chromatography) analysis at a concentration of 0.028% w/w ± (1.38%) in 500 mg capsules. After 12 weeks, a re-examination of IS levels and olfactory function was carried out.

**Statistical Analysis**

A normality test of the data distribution was conducted prior to the bivariate test, utilising the Kolmogorov-Smirnov method. A bivariate analysis was performed to ascertain the difference between before and after treatment, followed by multivariate analysis to determine the difference in changes (delta) between the three groups that would produce a significance value, stated as significant if the p-value <0.05 and continued with the Posthoc test using SPSS (Statistical Package for the Social Sciences).

## *Results*

Refer to Table 1. No significant variations in features were observed across the three groups for study (p=0.918; p=0.939; p=0.716; p=0.526).

Refer to Table 2. A notable reduction in the mean levels of indoxyl Sulphate (IS) was seen before and after treatment in the cohort administered 500 mg of curcumin (p = 0.008) and in the control or placebo group (p = 0.019). In olfactory discrimination and olfactory function (TDI), a significant difference was seen in the means between the group administered 1000 mg of curcumin (p = 0.001; p = 0.001) and the group administered 500 mg of curcumin (p = 0.003; p = 0.019). In olfactory identification, a significant change in the mean was seen between the group of patients administered 1000 mg of curcumin (p = 0.006). During the olfactory threshold assessment, no significant differences were seen in the mean values before and after treatment within any group (p = 0.164; p = 0.189; p = 0.383).

**Table 1.** Demographic Characteristics of Research Subjects

| Characteristics Demographics | Control (n=16) | Cur. 500 mg (n=16) | Cur. 1000 mg (n=16) | p |
|---|---|---|---|---|
| Gender, n (%) | | | | |
| Man | 9 (56.2) | 10 (62.5) | 9 (56.2) | 0.918[a] |
| Woman | 7 (43.8) | 6 (37.5) | 7 (43.8) | |
| Age, n (%) | | | | |
| 16-25 years | 1 (6.2) | 1 (6.2) | 1 (6.2) | |
| 26-35 years | 2 (12.5) | 2 (12.5) | 1 (6.2) | 0.939[b] |
| 36-45 years | 4 (25) | 4 (25) | 5 (31.2) | |
| 46-55 years | 9 (56.2) | 9 (56.2) | 9 (56.2) | |
| Length of CKD, n (%) | | | | |
| < 5 years | 7 (43.8) | 9 (56.2) | 9 (56.2) | 0.716[a] |
| >5 years | 9 (56.2) | 7 (43.8) | 7 (43.8) | |
| Urine, n (%) | | | | |
| Anuria | 6 (37.5) | 3 (18.8) | 5 (31.2) | 0.526[b] |
| Normouria | 3 (18.8) | 5 (31.2) | 1 (6.2) | |
| Oliguria | 7 (43.8) | 8 (50) | 10 (62.5) | |

[a]Chi Square, [b]Kruskal Wallis

**Table 2.** Differences in Mean: Levels of IS, Threshold, Discrimination, Identification, and Olfactory Function (TDI) Before and After Treatment

| | Group | Before Treatment | After Treatment | p |
|---|---|---|---|---|
| Level | Control | 1596.16 (260.92) | 1444.05 (259.69) | 0.019[a] |
| Indoxyl Sulphate, | Cur. 500 mg | 1506.82 (337.94) | 1322.62 (364.86) | 0.008[b] |
| ng/ml | Cur. 1000 mg | 1387.20 (326.89) | 1252.05 (387) | 0.114[a] |
| Threshold | Control | 6.75 (1.87) | 7.12 (1.96) | 0.164[a] |
| | Cur. 500 mg | 6.53 (2.23) | 7.06 (2.08) | 0.189[a] |
| | Cur. 1000 mg | 7.56 (2.22) | 7.75 (2.14) | 0.383[a] |
| Discrimination | Control | 6.31 (2.54) | 6.43 (2.25) | 0.697[a] |
| | Cur. 500 mg | 6.06 (2.29) | 8.62 (2.41) | 0.003[a] |
| | Cur. 1000 mg | 6.12 (0.95) | 9.43 (1.45) | 0.001[b] |
| Identification | Control | 6.18 (3.08) | 6.56 (3.09) | 0.083[a] |
| | Cur. 500 mg | 5.59 (3.28) | 6.06 (3.17) | 0.087[b] |
| | Cur. 1000 mg | 6.06 (1.94) | 6.57 (1.96) | 0.006[a] |
| Olfactory | Control | 19.25 (6.82) | 20.12 (6.56) | 0.089[a] |
| Function | Cur. 500 mg | 18.18 (7.17) | 21.75 (6.73) | 0.019[a] |
| | Cur. 1000 mg | 19.75 (4.41) | 23.75 (4.75) | 0.001[a] |

Data are presented with mean (SD); [a]T Dependent, [b]Wilcoxon Normal values: threshold >6.5; discrimination ≥11; identification ≥12; olfactory function ≥30

**Table 3.** Differences in Mean Changes in IS Levels, Threshold, Discrimination, Identification, and Olfactory Function (TDI) Before and After Treatment

| | Group | Delta | p | Post-hoc | |
|---|---|---|---|---|---|
| | | | | Cur. 500 mg | Cur. 1000 mg |
| IS Level | Control | -154.10 (235.47) | 0.870[a] | | |
| (ng/ml) | Cur. 500 mg | -184.20 (225.20) | | | |
| | Cur. 1000 mg | -135.14 (322.04) | | | |
| Threshold | Control | 0.37 (1.02) | 0.636[b] | | |
| | Cur. 500 mg | 0.53 (1.54) | | | |
| | Cur. 1000 mg | 0.18 (0.83) | | | |
| Discrimination | Control | 0.125 (1.25) | 0.001[a] | 0.001[c] | 0.001[c] |
| | Cur. 500 mg | 2.56 (1.41) | | | 0.295[c] |
| | Cur. 1000 mg | 3.31 (1.07) | | | |
| Identification | Control | 0.37 (0.80) | 0.618[b] | | |
| | Cur. 500 mg | 0.46 (1.02) | | | |
| | Cur. 1000 mg | 0.50 (0.63) | | | |
| Olfactory | Control | 0.875 (5.14) | 0.002[a] | 0.010[c] | 0.002[c] |
| Function | Cur. 500 mg | 3.56 (1.92) | | | 1,000[c] |
| | Cur. 1000 mg | 4.00 (1.86) | | | |

Data are presented as mean (SD); [a]One Way ANOVA, [b]Kruskal Wallis, [c]Bonferonni

Table 3 reveals significant differences in the changes (delta) in olfactory discrimination (p = 0.001) and olfactory function (p = 0.002) among the three study groups. The Post Hoc-Bonferroni Test indicated significant differences in discrimination between the 1000 mg curcumin group and the control (p = 0.001), as well as between the 500 mg curcumin group and the control (p = 0.001). Olfactory function was significantly enhanced in the 1000 mg curcumin group compared to control (p = 0.002) and in the 500 mg curcumin group compared to control (p = 0.010). Nonetheless, no substantial variations in alterations (delta) were observed in Indoxyl Sulphate levels, olfactory threshold, and olfactory identification before and after treatment between the three study groups (p = 0.870; p = 0.636; p = 0.618).

**Table 4.** Correlation of Indoxyl Sulphate Values with Olfactory Function, Duration of CKD, and Urine Volume

| **Indoxyl Sulphate** | **n = 48** | **n = 48** |
|---|---|---|
| | **r value** | **p-value** |
| Olfactory Function | -0.509 | 0.075 |
| Duration of CKD | 0.580 | 0.364 |
| Urine Volume | -0.703 | 0.004 |

Table 4 indicates an absence of significant link between indoxyl sulphate levels and function of smell (r = -0.509; p = 0.075), as well as between indoxyl sulphate levels and the duration of chronic kidney disease (CKD) (r = 0.580; p = 0.364). There exists a substantial association between indoxyl sulphate concentrations and urine volume (r = -0.703; p = 0.004).

## *Discussion*

Uremia can impact olfactory epithelium neurones in both peripheral and central routes. Olfactory epithelial neurones experience perpetual renewal throughout life. Consequently, any poison that inhibits or ceases cellular proliferation can disrupt olfaction. Uremic contaminants that compromise the essential antioxidant system of the olfactory tract epithelium and bulb of olfactory have previously been shown to significantly reduce olfactory function (2). Indoxyl Sulphate is a bound to protein uremic toxicity molecule and is considered a risk factor for disease development in individuals with long-term kidney disease. Indoxyl sulphate promotes the production of reactive oxygen species (ROS) via activating NADPH oxidase (NOX) in mitochondria and plasma membranes, alongside the stimulation of the Nuclear Factor kappa B (NFκB) cascade and the translocation of activating protein 1 (AP1), owing to the prooxidative and proinflammatory effects elicited by Indoxyl sulphate (9, 10). Curcumin plays a significant role in disease prevention due to its efficacy as a reactive oxygen species scavenger and its capacity to modulate biological processes. Curcumin has been demonstrated to contribute to the suppression of both acute and chronic inflammation through its inhibitory effects on enzymes like COX-2. Curcumin consumption has been associated with decreased levels of tumor necrosis factor-alpha (TNF-α), interleukin-6, and monocyte chemoattractant protein-1 (8).

The results of this study indicate that most of the patients' gender in the control group, the 500 mg curcumin group, and 1000 mg were male, the age of patients in the control group, the 500 mg curcumin group, and 1000 mg were mostly in the age range of 46-55 years. No substantial variation in gender and age of patients was seen across the three study groups (p>0.05). The 11th Report of the Indonesian Renal Registry indicates that the prevalence of chronic kidney disease (CKD) among males in Indonesia surpasses that of women, with the majority of patients falling within the 45-64 age bracket (11). This study indicates that patients under 25 years of age comprised 6.3%, highlighting the necessity to focus on kidney health among this demographic. In the control group, the duration of chronic kidney disease for the majority of patients exceeded 5 years, comprising 9 individuals (56.2%); conversely, in the 500 mg and 1000 mg curcumin groups, the length was less than 5 years, also totalling 9 individuals (56.2%). The urine volume of patients with chronic renal disease was predominantly

observed in the control group, whereas the curcumin 500 mg and curcumin 1000 mg groups exhibited oliguric conditions. Urine volume and the length of chronic renal disease did not differ statistically significantly between the three study groups (p>0.05). The length of chronic renal illness and volume of urine with olfactory anomalies did not significantly correlate, according to this study. Indoxyl sulphate levels and urine volume were significantly correlated in patients with a long-term kidney disease. These results support the theory that the body's buildup of uremic toxins may result from the kidneys' poor ability to eliminate metabolic fluids as a result of chronic kidney disease. Uremic pollutants are chemicals that are normally filtered by healthy kidneys, as reported by Vanholder et al. Following diminished kidney function, toxins accumulate in the body and adversely affect biological processes (12).

Indoxyl sulphate is a chemical polycyclic aromatic anion molecule resulting from the metabolic processes of tryptophan derivatives, which are transformed into indole through the enzymatic action of tryptophanase produced by gut microbiota, including Escherichia coli. Indoxyl sulphate possesses a molecular mass of 213 Da and exhibits a binding affinity of at least 90% to albumin. The hemodialytic clearance of the drug is comparatively inferior than physiological clearance (13). Syafrita et al. reported that the mean indoxyl sulphate concentration in healthy individuals was 6.02 ± 1.82 ng/ml. A notable disparity in indoxyl sulphate concentrations was observed among CKD patients and healthy subjects, where indoxyl Sulphate levels in CKD patients increased 19 times compared to healthy subjects (14). In this study, the average IS levels before and after treatment were very high in CKD patients. Indoxyl Sulphate (IS) levels were significantly lower before and after administration in both the control group (p = 0.019) and the group of patients administered 500 mg curcumin (p = 0.008). In contrast, the group of individuals who received 1000 mg of curcumin showed a non-significant decrease in IS levels (p = 0.114).

However, the differences in Indoxyl Sulphate (IS) levels between the three treatment groups before and after therapy were not statistically significant (p = 0.870).

24 patients with long term renal disease participated in a study conducted by Pivari et al., administered 500 mg of curcumin for 3 and 6 months reported a substantial reduction in plasma p-cresol levels. However, plasma IS concentrations did not increase in the group given supplements, this indicates that the administration of curcumin maintains IS levels from increasing (15).

Guidelines for dietary protein limitation in people with chronic kidney disease to alleviate symptoms caused by the buildup of uremic contaminants from the breakdown of externally consumed protein have existed for over a century. These ideas were fervently promoted during the initial period when dialysis services were neither available nor accessible. The widespread availability of dialysis services has led to a progressive decline in interest regarding dietary protein limitation for persons with chronic kidney disease (CKD). Dietary protein restriction is a fundamental therapeutic approach in adults with chronic kidney disease (CKD) to decelerate disease development, with numerous specialists advocating for a diet with limited protein for CKD patients (16). Other studies have shown that patients who adhere to CKD guidelines experience fewer side effects, including increased uremic toxins. Specifically, higher compliance with serum electrolyte management and other metrics has been associated with better renal outcomes and lower uremic toxin levels (17); the above theory suggests that the indoxyl Sulphate levels in the 1000 mg curcumin group were not significant due to poor patient compliance in that group with their daily dietary management.

In this study, there was no relationship between indoxyl Sulphate levels and olfactory disorders in CKD patients with hemodialysis. By research conducted on hemodialysis patients showed a relationship between changes in the smell test and clinical parameters of malnutrition. Still, no relationship was found with levels of uremic toxins such as monomethylamine, ethylamine, indoxyl Sulphate, and P-cresol Sulphate (7).

The 1000 mg and 500 mg curcumin groups in this study showed a significant difference in olfactory discrimination (p=0.001 and p=0.003, respectively), while the three study groups showed a significant difference in change (delta) (p=0.001). The 500 mg curcumin group

(p = 0.019) and the 1000 mg curcumin group (p = 0.001) differed significantly in the olfactory function. The three study groups showed a significant difference in change (delta) (p = 0.002). The Post Hoc-Bonferroni Test was then used to identify the difference between the two groups, and the discrimination between the 1000 mg curcumin group and the control group was found to be significant (p = 0.001). The olfactory function was found to be significant in the 500 mg curcumin group with the control (p = 0.001), in the 1000 mg curcumin group with the control (p = 0.002), and in the 500 mg curcumin group with the control (p = 0.010). There was no significant difference in change (delta) between the three study groups (p=0.618), but there was a significant difference in identification (p=0.006) in the group of participants given 1000 mg curcumin. Each group's olfactory threshold did not significantly change before or after treatment, and the three study groups did not significantly differ in change (delta) (p=0.636).

Almost all components of olfactory function decreased found in this study (normal value of olfactory function ≥30; threshold >6.5; discrimination ≥11; identification ≥12) found olfactory disorders in chronic kidney disease patients are limited to olfactory discrimination and identification functions, with threshold functions still within normal limits. The pattern of olfactory abnormalities in chronic kidney disease patients indicates the investigation of odor discrimination and identification transpires within the central route. The assessment of olfactory threshold, on the other hand, reflects the peripheral olfactory tract. The study by Sagar et al. involved 136 patients with chronic kidney disease (CKD), the majority of olfactory abnormalities were related to olfactory identification. The olfactory threshold exhibited superior performance compared to olfactory identification (18).

A research by Frasnelli et al. similarly observed that haemodialysis patients with olfactory problems exhibited significantly decreased discriminating and recognition capabilities, while their olfactory threshold values remained unaffected. This finding raises speculation that olfactory dysfunction in chronic kidney failure patients begins at the central nervous level (19,20).Until now, there has only been one study similar to this one, conducted by Malekmakan et al., which examined the effects of curcumin on olfactory function in CKD patients. In this study, CKD patients were given 1000 mg of curcumin for 12 weeks and olfactory training twice a day for 12 weeks to improve olfactory function. The study found that both had an improving effect on the olfactory function of CKD patients (21).

Curcumin, a conventional medicinal compound with diverse biological properties, has been employed by numerous researchers to address various disorders; it enhances the proliferation and survival of olfactory ensheathing cells in both normoxic and hypoxic environments. Curcumin also promotes olfactory ensheathing cell migration and phagocytic activity. Curcumin has an impact on these cells' vitality, while hypoxia reduces it. Curcumin influences the physiological behaviour of olfactory ensheathing cells in vitro, enhancing their regenerative capabilities upon in vivo transplantation, potentially impacting cellular migration, axon regeneration, remyelination, and recovery of function at the injury site (22). Curcumin also inhibits certain pathways associated with renal impairment. The renoprotective effect of curcumin is linked to the mitigation of three primary factors: firstly, the mitigation of the effects of oxidative stress through the inhibition of O2- production and the scavenging of other reactive oxygen species; secondly, the prevention of Nrf2 degradation via the proteasomal ubiquitin pathway, resulting in elevated levels of antioxidant enzymes. Third, curcumin can diminish the inflammatory process by inhibiting inflammatory transcription molecules such as NF-kB and TNF-a (23).

Human studies have demonstrated that curcumin can have an immunosuppressive effect by inhibiting NF-kB and suppressing the initiation of Th1 cytokines in peripheral blood lymphocytes, which are typical in kidney transplant recipients. A dose of curcumin diluted to 10 µl is equivalent to a dose of curcumin 0.01 ml (24).

Research by Khajehdehi et al. involving 40 chronic kidney disease patients administered 500 mg of curcumin for 2 months demonstrated a reduction in TGF-β and IL-8 levels, as well as a drop in proteinuria levels (25).

Curcumin enhances the activity of the catalase

(CAT), enzymes glutathione peroxidase (GPX), glutathione reductase, and superoxide dismutase (SOD) in 50 patients with chronic kidney disease (CKD) undergoing haemodialysis (26). In line with research conducted on mice to ascertain the impacts of curcumin on mice transplanted, Olfactory Ensheating Cells on the injured spine can repair the injury by obstructing the stimulation of nuclear factor kappa beta (NF- kB) (27).

Likewise, research states that curcumin has been proven to suppress the occurrence of toxicity in the kidneys by inhibiting oxidative injury and restoring the antioxidant enzyme profile in the kidneys of mice injected with gentamicin. Research evidence shows that the curcumin diet given to mice can protect kidney cells against oxidative stress. This improvement is expected to reduce oxidative stress that damages the olfactory signaling pathway, thereby inducing improvement in olfactory function (28).

**Study Strengths and Limitations**

This study possesses multiple strengths, notably its randomised controlled trial design with comparable baseline characteristics across groups, which strengthens internal validity and supports causal interpretation of the findings. The use of standardized and validated olfactory assessments (Sniffin' Stick Test) together with biochemical measurement of plasma indoxyl Sulphate provides a comprehensive evaluation of both functional and molecular outcomes. In addition, the inclusion of two different curcumin doses allows assessment of a potential dose–response relationship in patients with stage V chronic kidney disease undergoing regular hemodialysis. This study, however, possesses challenges. The small number of subjects and single-center methodology may restrict generalisability. Furthermore, the study duration was limited to 12 weeks, and other uremic toxins potentially affecting olfactory function were not evaluated. Future studies with larger, multicenter populations, longer follow-up, and broader toxin profiling are warranted.

## *Conclusion*

Curcumin administration has an effect on improving olfactory function in CKD patients, and no deterioration of indoxyl sulphate levels occurred, suggesting that curcumin can sustain IS levels to prevent elevation. Further research is needed to compare with this study.

**Conflict of Interest**

All authors affirm that we possess no affiliations or engagements with any organization or institution that has financial or non-financial interests in the topic matter or materials addressed in this paper.

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