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# Meta-analysis investigating the impact of a phosphate-specific diet on serum phosphate levels in patients undergoing hemodialysis

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**ABSTRACT** We conducted a meta-analysis to assess the impact of a phosphate-specific diet on the serum phosphate levels of individuals undergoing hemodialysis. Methods a systematic literature search was conducted until November 2021, resulting in the inclusion of 14 studies comprising 1284 adults undergoing hemodialysis at the study's commencement. Among them, 671 were assigned to a phosphate-specific diet group, while 613 served as the control. The researchers documented correlations between the effects of a diet focused on phosphates and the levels of phosphates in the blood of persons who were undergoing hemodialysis. Employing the contentious method with a random or fixed-effect model, we computed the mean difference (MD) along with 95% confidence intervals (CIs) to evaluate the effect of a phosphate-specific diet on serum phosphate levels in this population. In adults undergoing hemodialysis, a phosphate-specific diet exhibited a significantly more favorable change in serum phosphate levels (MD, -0.66; 95% CI, -0.95 to -0.36,  $p < 0.001$ ), accompanied by moderate heterogeneity ( $I^2 = 71\%$ ) when compared to the control group. In adults undergoing hemodialysis, a phosphate-specific diet resulted in a significantly reduced change in serum phosphate levels compared to the control. Additional studies are needed to confirm these findings and enhance confidence in the results.

**INDEX TERMS** phosphate-specific diet; hemodialysis; control; serum phosphate levels change.

## I. INTRODUCTION

Extra dietary phosphate consumption possibly adds to cardiovascular and bone diseases in subjects with chronic kidney disease. [1] Chronic kidney disease-mineral and bone disease characterize cardiovascular and bone disorders in individuals with chronic kidney disease. The metabolic disturbances in calcium and phosphate metabolism play a role in these outcomes.[2] According to the 2020 Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Nutrition in chronic kidney disease, individuals with stages 3a–5D chronic kidney disease are recommended to adjust their dietary phosphate intake to maintain serum phosphate within the normal range (Grading of Recommendations, Assessment, Development, and Evaluations evidence 1B). [3] To address hyperphosphatemia while managing other complications associated with dietary issues, dietitians implemented dietary interventions tailored to the individual's specific needs, preferences, and capabilities. [4] The primary component of

the prescribed diet for individuals with kidney disease is the restriction of dietary phosphate, and it stands as a key focus in counseling sessions conducted by kidney dietitians.[5] However, even in hemodialysis clinics where kidney dietitians are available, individuals exhibit a lack of information and encounter difficulties in adhering to nutrient guidelines, particularly in relation to phosphate, [6, 7] and Roughly half of the individuals undergoing hemodialysis experience predialysis hyperphosphatemia, characterized by serum phosphate levels exceeding 5.5 mg/dl.[8, 9] Considering the constraints on dietitian time [10] and the persistence of hyperphosphatemia, there is a need to explore the effectiveness of phosphate-specific dietary interventions and their potential impact on improving serum phosphate levels in this population. This meta-analysis sought to assess the impact of a phosphate-specific diet on serum phosphate levels in adults undergoing hemodialysis.

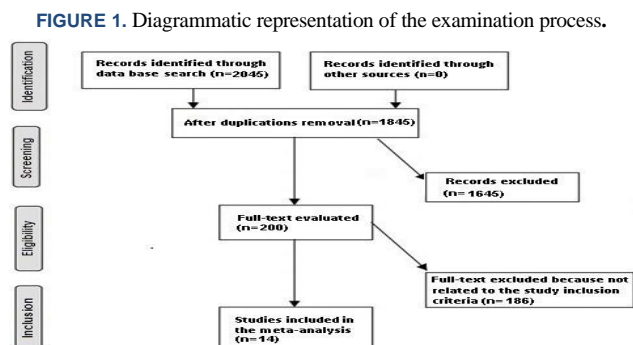
## II. METHODOLOGY

### A. STUDY SELECTION

The primary aim of this study is to examine the impact of phosphate-specific dietary intake on serum phosphate levels in individuals undergoing hemodialysis. Utilizing tools such as odds ratio (OR), frequency rate or relative risk, and a 95% confidence interval, the search was limited to studies conducted in English. Inclusion criteria were not restricted by study type or size. Studies lacking correlation, such as editorials, perspectives, letters, and commentary, were excluded from the analysis. Figure 1 exhibits the mode of analysis. The article inclusion criteria are classified and integrated into meta-analysis when the research design included a randomized controlled trial, a prospective study, or a retrospective study. The study focused on individuals undergoing hemodialysis. The intervention involved a phosphate-specific dietary intake. The study involved comparisons between the effects of phosphate-specific intake and a control group. The following exclusion criteria were adopted among the intervention groups. Studies that did not investigate the impact of phosphate-specific dietary intake on serum phosphate levels in individuals undergoing hemodialysis. Studies with interventions other than phosphate-specific dietary intake. Studies that did not specifically focus on comparative outcomes.

### B. DATA POOLING

Various clinical outcomes emerged when comparing traditional herbal medication to standard care in the treatment of burn wound ulcers. The primary inclusion criterion in these findings was the healing time. Language restrictions were not considered when screening candidates and determining which study to include. The trials did not impose any restrictions on the number of people that might be recruited. The synthesis conducted in our study eliminated reviews, editorials, and letters due to their lack of intervention. The comprehensive procedure for examination identification is outlined in Figure 1.



## III. IDENTIFICATIONS OF STUDIES

The search strategy followed the PICOS principle [12], outlining critical elements as P (population): individuals undergoing hemodialysis; I (intervention/exposure): phosphate-specific intake; C (comparison): phosphate-specific intake and control; O (outcome): change in serum phosphate levels; and S (study design): with no limitations [13]. A systematic and concise search was conducted on MEDLINE/PubMed, Google Scholar, Embase, OVID, and Cochrane Library until November 2021. The search involved a combination of keywords and related terms for phosphate-specific intake, hemodialysis, control, and change in serum phosphate levels, as detailed in Table 1. The chosen studies were compiled in EndNote software to eliminate duplicates. Furthermore, a comprehensive screening of the titles and abstracts was conducted to remove any data that did not demonstrate the impact of phosphate-specific intake and control on the outcomes studied in individuals undergoing hemodialysis. Relevant information was extracted from the remaining studies.

TABLE I  
Database Search Technique for Examining Content

Database	Search strategy
Google Scholar	#1 "burn wound ulcer" OR "wound healing time" #2 "traditional herbal medicine" OR "Basic Fibroblast Growth Factor" #3 #1 AND #2
Embase	#1 'burn wound ulcer' /exp OR 'wound healing time' #2 'traditional herbal medicine'/exp OR 'Basic Fibroblast Growth Factor' / #3 #1 AND #2
Cochrane library	#1 (burn wound ulcer):ti,ab,kw (wound healing time):ti,ab,kw (Word variations have been searched) #2 (traditional herbal medicine):ti,ab,kw OR (Basic Fibroblast Growth Factor):ti,ab,kw (Word variations have been searched) #3 #1 AND #2
Pubmed	#1 "burn wound ulcer"[MeSH] OR "wound healing time"[All Fields] #2 "traditional herbal medicine"[MeSH Terms] OR "Basic Fibroblast Growth Factor"[All Fields] #3 #1 AND #2
OVID	#1 "burn wound ulcer"[All Fields] OR "wound healing time" [All Fields] #2 "traditional herbal medicine"[ All fields] OR "Basic Fibroblast Growth Factor"[All Fields] #3 #1 AND #2

## IV. SCREENING OF STUDIES

Subject-related and study-related characteristics of the data are taken into account for the collection and categorization of information, which is then organized into a standardized format. The categorization includes standard elements such as the last name of the first author, trial duration, practice location, study design, subject type, sample size, categories,

demography, treatment methodology, information source, evaluation method (both qualitative and quantitative), statistical analysis, and primary outcome assessment [12]. The assessment of methodological quality utilized the "risk of bias tool," adopted from the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. This meta-analysis suggests that in cases where a trial meets the previously mentioned standards for inclusion criteria, any conflicts arising during data collection by two reviewers should be resolved through discussion. If necessary, the "corresponding author" should be involved to ensure the quality of the methodology. [14].

## V. STATISTICAL ANALYSIS

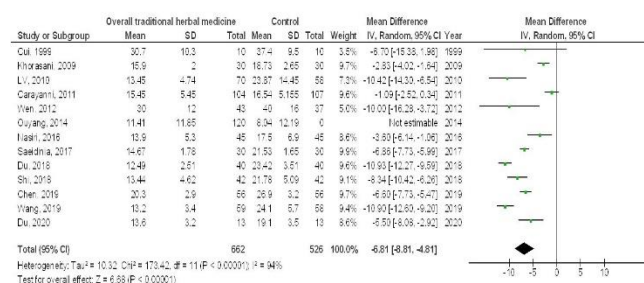
The present meta-analysis involved the calculation of odds ratio (OR) and mean difference (MD) along with a 95% confidence interval (CI). These calculations were performed using random- or fixed-effect models for dichotomous or continuous data, respectively. The researchers utilized the I<sup>2</sup> index, which ranges from 0 to 100, to evaluate the level of heterogeneity. Higher values on the I<sup>2</sup> index indicate greater heterogeneity, whereas an I<sup>2</sup> value of 0 indicates the absence of heterogeneity. The choice to utilize a random effect model was made in response to the I<sup>2</sup> statistic surpassing or equaling 50%. In contrast, when the value of I<sup>2</sup> was less than 50%, there was a stronger inclination towards favoring the fixed effect [6]. As mentioned before, the results of the initial inquiry were categorized using subcategory analysis. The evaluation of publication bias was conducted by the utilization of Begg's and Egger's tests for quantitative analysis. The identification of publication bias was determined if the p-value above 0.05. The p-values were computed by a two-tailed analysis. Graphs and statistical analysis were conducted using Jamovi 2.3.ve 0.05. The p-values were computed by a two-tailed analysis. Graphs and statistical analysis were conducted using Jamovi 2.3.

## VI. RESULTS

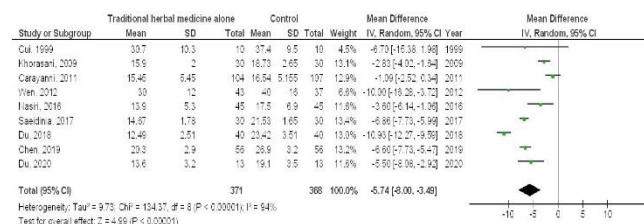
Out of a total of 2045 unique studies identified, 14 studies meeting the inclusion criteria and spanning the period from 2003 to 2021 were included in the study. [16-29] This meta-analysis, derived from 14 studies, encompassed a cohort of 1284 adults undergoing hemodialysis at the study's commencement. Among them, 671 were assigned to a phosphate-specific diet, while 613 served as the control group. All the studies examined the impact of a phosphate-specific diet on serum phosphate levels in adults undergoing hemodialysis. The size of the study varied, encompassing a range of 30 to 297 adults undergoing hemodialysis at the initiation of each study. Details of the 14 studies are presented in Table 2. In adults undergoing hemodialysis, the serum phosphate levels exhibited a significantly more favorable

change with a phosphate-specific diet (MD, -0.66; 95% CI, -0.95 to -0.36,  $p < 0.001$ ), demonstrating moderate heterogeneity ( $I^2 = 71\%$ ) compared to the control, as depicted in Figure 2. Stratified analysis in studies, which considered adjustments for gender, ethnicity, and age, was not conducted due to the absence of information on these factors in the included studies. Both visual inspection of the funnel plot and quantitative assessment using the Egger regression test indicated no evidence of publication bias ( $p = 0.87$ ). However, most of the studies incorporated in the analysis exhibited low procedural quality primarily due to their limited sample size. None of the studies demonstrated selective reporting bias, and there were no instances of incomplete outcome data or selective reporting.

**FIGURE 2.** A forest plot of the serum phosphate levels change in adults undergoing hemodialysis with the phosphate-specific diet compared to the control.



**FIGURE 3.** The effect's forest plot of the traditional herbal medicine alone



compared to standard treatment on wound healing time in personals with burn wound ulcers.

TABLE II  
Characteristics of Studies

Study	Country	Total	Traditional Chinese medicine	Control
Cui, 1999 <sup>7</sup>	China	20	10	10
Khorasani, 2009 <sup>8</sup>	Iran	60	30	30
LV, 2010 <sup>9</sup>	China	128	70	58
Carayanni, 2011 <sup>10</sup>	Greece	211	104	107
Wen, 2012 <sup>11</sup>	China	80	43	37
Ouyang, 2014 <sup>12</sup>	China	240	120	120
Nasiri, 2016 <sup>13</sup>	Iran	90	45	45
Saeidinia, 2017 <sup>14</sup>	Iran	60	30	30
Du, 2018 <sup>15</sup>	China	80	40	40
Shi, 2018 <sup>16</sup>	China	84	42	42
Chen, 2019 <sup>17</sup>	Korea	112	56	56
Wang, 2019 <sup>18</sup>	Korea	117	59	58
Du, 2020 <sup>19</sup>	China	26	13	13
	<b>Total</b>	<b>1282</b>	<b>649</b>	<b>633</b>

## VII. CONCLUSION

The present meta-analysis included a total of 13 examinations conducted between 1999 and 2020. Out of these examinations, 549 utilized traditional herbal medicine as a treatment approach, while 633 employed modern treatments. The study's sample size ranged from 20 to 240 individuals [7-19]. The findings from the data analysis suggest that the use of traditional herbal medicine, either alone or in combination with Basic Fibroblast Growth Factor, led to a notable reduction in the duration of wound healing for burn wound ulcers when compared to the conventional therapy approach. Nevertheless, it is crucial to exercise prudence when interpreting these findings, given that a significant portion of the chosen studies had a limited sample size (8 out of 13 investigations had a sample size greater than 100). Burn sufferers frequently experience scarring, discomfort, and itching, and healing takes longer the more extensive the burn's damage is. Infection risk is increased in burns that take longer than 2-3 weeks to re-epithelialize. Additionally, there is a very good chance that it will develop into a hypertrophic scar, thus skin transplant surgery is frequently used to treat it. This is why it is thought that the most often utilized markers to evaluate the efficacy of burn treatment were wound recovery time, pain, and scar formation rate. Based on these findings, herbal medicine created by mixing many medications might be thought of as more helpful in shortening wound recovery time than a single medication when the burn area is not extensive. In light of the aforementioned research findings, it

is evident that complex drug treatments involving many herbal medicines are more effective than single drugs, and that treatment utilizing herbal medicine has a substantial impact on the treatment of burn patients. Additionally, herbal medicine treatments were typically highly efficient at reducing pain around the wound. One of the most frequent side effects that burn patients experience is pain [20], and pain in burn patients is not only brought on by the injury itself but also by interventional treatments such as surgical treatment, eschar removal, and wound cleaning [21]. Additionally, if patients are suffering from psychological illnesses such as severe anxiety and depression, dressings must be applied every day when the pain is not well controlled. Therefore, it's crucial to manage discomfort during treatment. It was notable that the Basic Fibroblast Growth Factor was frequently used combined use of herbal medicine and Western medicine. These studies sprayed Basic Fibroblast Growth Factor on the wound area, which is crucial for the development of wound granulation tissue and the regeneration of capillaries and nerves. It was employed to encourage window surface union. It is believed that herbal remedies or treatments with comparable efficacy can be used in place of or in addition to the Basic Fibroblast Growth Factor to produce the following synergistic effect [22]. It is possible to use oral drugs to actively restore this and encourage regeneration because there is a large fluid loss after a burn in addition to a generalized drop in immune function. By correctly diluting it to the intended use and the patient's physical condition, it can be used in treatments for things like clearing heat, oxidizing blood vessels, purifying the diaphragm, and treating inflammatory illnesses [23]. Due to edema, congestion, and exudative fluid in the capillary walls beneath the dermis in severe burn regions, swelling and tension of the window surface and surrounding tissues rise, creating a vicious cycle of "external pressure" and "internal blockage" in the window surface microcirculation. Due to this, it is challenging for oral medications to reach an effective concentration in the area around the local wound [24]. As a result, one might attempt herbal acupuncture, which is a technique for delivering the drug close to the wound area. Drugs employed as intervention strategies in the control group, in addition to Basic Fibroblast Growth Factor, included silver sulfadiazine 1% cream applied eight times, rifampicin once, and bepanthenol cream once. Ointments containing antibiotics like silver sulfadiazine or rifampicin are frequently used for their antibacterial effects since burn wounds are susceptible to infection. However, there are reports that topical silver-containing medications, such as silver sulfadiazine ointment, can hinder wound healing [25] and that, after prolonged use, bacteria become resistant to the medication's sterilizing effects and the quantity of wound-infecting microbes increases. Additionally, hepatic and nephrotoxicity,

as well as leukopenia, may arise in the event of wounds with a significant surface area. Dexpanthenol, the primary component, is absorbed via the skin and changed into pantothenic acid, which is a part of coenzyme A, a coenzyme that is crucial for cell metabolism. Coenzyme A is only effective as an adjunctive treatment for sunburn since it aids in the synthesis of substances that rebuild damaged skin tissue but does not relieve pain or inflammation [26]. Dressings of all kinds have recently been created and utilized to make up for these inadequacies. The meta-analysis had certain limitations: There might be an assortment bias due to the exclusion of some selected studies; however, these excluded studies did not meet the criteria for inclusion in the meta-analysis. Furthermore, we required additional data to assess whether variables such as age, gender, and ethnicity influenced the results. The objective of the meta-analysis was to investigate the conventional treatment of individuals with burn wound ulcers involving traditional herbal medicine. The utilization of erroneous or incomplete data from a previous study may have enhanced bias. The predominant elements that can contribute to instances of prejudice encompass the individual's nutritional state, in conjunction with their ethnic background, gender, and age. The fluctuation of values can occur inadvertently as a result of inadequate data and the omission of certain unpublished investigations.

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