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IMPACT OF FOOD AND DRINKS ON URINE PRODUCTION: A SYSTEMATIC REVIEW

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IMPACT OF FOOD AND DRINKS ON URINE PRODUCTION: A SYSTEMATIC REVIEW

ABSTRACT

Context: The impact of food and drinks on body fluid metabolism is of direct clinical relevance but current evidence remains fragmented. **Aim:** Synthesize current evidence on the role of food and

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drinks in urine production. **Methods:** Systematic review as per PRISMA guidelines using MEDLINE and EMBASE databases (completed October 2019). Studies reporting on the effect of food, food constituents, and drinks on urine production were included. Two authors performed an independent extraction of relevant articles using predetermined datasets and completed quality-of-study indicators. **Results:** A total of 49 studies were included, of which 21 enrolled human subjects, and 28 were clinically- relevant animal studies (all of which utilized rodent models). The included studies were determined to be of variable quality. High dietary sodium, as well as wine, spirits, high-caffeine coffee, and caffeinated energy drinks, increased urine production in human studies. Decreased urine production was associated with low dietary sodium and consumption of milk, orange juice, and high-salt/high-sugar drinks. In animal models, a variety of fruits, vegetables, herbs, spices, and honey were associated with increased urine production. **Conclusion**: Current evidence suggests that although several types of food and drinks may impact body fluid metabolism, the quality of the data is variable. Urine production appears to be influenced by multiple factors including composition (i.e., moisture, macronutrients, and electrolytes), metabolite load, and the presence of specific diuresis-promoting substances (e.g., caffeine, alcohol) and other bioactive phytochemicals. Future research is needed to support current evidence and the physiologic mechanisms underlying these findings.

Key words: Food, Drinks, Nutrients, Renal excretion, Urine, Fluid balance, Polyuria, Diuresis

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Review Criteria

- Systematic review as per PRISMA guidelines using MEDLINE and EMBASE databases.
- Comparative (randomized controlled trials [RCTs] and non-RCTs) human and animal studies reporting on the effect of food, food constituents, and drinks on urine production were included.
- Two authors performed an independent extraction of relevant articles using predetermined data sets and completed quality-of-study indicators.

Message for the Clinic

- Current evidence suggest that several types of food and drinks may impact body fluid metabolism the quality of the data is variable.
- Urine production appears to be influenced by multiple dietary factors including food composition (i.e., water, macronutrients, and electrolytes), metabolite load, and the

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presence of specific diuresis-promoting substances (e.g., caffeine and alcohol) and other bioactive phytochemicals.

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INTRODUCTION

Polyuria is defined by the International Continence Society as excess urine production (1). Polyuria is among the most common and bothersome urinary conditions in the general population—particularly in the context of nocturnal polyuria (i.e., excess urine production during the main sleep period) (1), which is thought to be the most common cause of nocturia overall (2).

Dietary fluid load, as a cumulative function of the volume of all drinks consumed throughout day, is strongly correlated with urine volume (3) and thus receives considerable attention in the polyuria patient interview. However potential differences in the diuretic properties of specific drinks, as well as possible complex influences from food consumption, are often overlooked. Foods, although highly variable across cultures and cuisines, may account for upwards of 20% of total daily fluid intake in the form of water in food (4). Moreover, total urine volume is a function of urinary solute excretion which, in turn, is primarily determined by the concentrating ability of the kidney in conjunction with macronutrients, minerals, and metabolites (e.g., urea) derived from food consumption (4). Alternatively, specific compounds in foods may also exert a direct diuretic effect, as widely recognized by traditional medical practices across the world, which have long employed foods and herbal remedies in the treatment of edema, hypertension, and a variety of urinary disorders (5–7).

Beyond a rudimentary assessment of total water load, the more complex role of the types of food and drinks, in the pathogenesis of polyuria, has begun to garner greater attention in current International Continence Society practice recommendations, including a multidisciplinary Delphi panel consensus statement on the importance intake diaries which incorporate foods and caloric intake (in addition to fluids) in the evaluation and management of nocturia (8). Consistently, multinational practice survey data on the treatment of nocturia in the United States and Europe suggest that initial lifestyle and behavioral counselling may include avoidance of certain foods, alcohol, and caffeine in addition to more general recommendations regarding absolute water intake (9).

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Despite these recent practice trends, more detailed evidence regarding individual foods, food constituents, and drinks in the pathogenesis of polyuria is fragmented, and specific dietary guidelines for nocturia are not available from the International Continence Society (8). Likewise, the European Food Safety Authority (EFSA), recognize that the precise physiological relationship between foods/food constituents and renal water elimination in humans remains poorly defined (10). However, preliminary evidence regarding the mechanistic relationship between individual foods, food constituents, and drinks may be extrapolated from clinically relevant animal studies, wherein a growing number of animal models have employed and refined a "diuretic index" (i.e., ratio of urine excretion in a test group to a control group) to quantitatively assess diuretic activity (11–17). Accordingly, this review aims to synthesize available evidence regarding the role of food, food constituents, and drinks on urine production in both humans and animals, which may be of direct clinical relevance in the first-line behavioral management of polyuria.

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METHODOLOGY

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (18).

Eligibility criteria

Populations and Types of studies/Interventions

Comparative (randomized controlled trials [RCTs] and non-RCTs) human and animal studies investigating the diuretic effect of specific orally-ingested foods, food extracts/herbal teas, and drinks were included. Studies performed on medicinal plants without any food use or single phytochemicals isolated from plants were not included. Plant materials which are not typically known as food, were checked for their food use referring to www.wikipedia.org (Supplementary data 1).

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Outcomes

The primary outcome was the effect of food, food extracts/nutrients, and drinks on urine volume (UV). Specific effects of these substances on urinary sodium (UNa^+), potassium (UK^+), and chloride (UCl^-) excretions were also recorded when available.

Search strategy

The MEDLINE and EMBASE databases were searched with no restriction on publication date. The search was completed in October 2019. Only English-language studies were included. The complete search strategy is outlined in Supplementary Data 1.

Data collection and analysis

Two review authors (U.S.A., R.H.) independently screened the abstracts of all publications rendered by the predefined search criteria. The full text of potentially eligible research items was evaluated and abstracted using a standardized spreadsheet to capture information on study design, specific exposures, and outcomes. The risk of bias was assessed using RoB 2.0 (Risk-of-Bias tool for cross-over trials) (19) and SYRCLE's RoB (SYRCLE's risk of bias tool for animal studies) (20) tools.

RESULTS

The study selection process is outlined in Figure 1. A total of 49 studies met the criteria for inclusion. Twenty-one human studies evaluated the effect of dietary sodium, sports drinks, meat, sugars/sweeteners, milk/milk-based drinks, tea, coffee, alcohol, and energy drinks on urine volume (UV). Twenty-eight animal studies assessed the effect of honey, fruits, vegetables, herbs, and spices on UV. All 28 animal studies employed rodent models. All results are reported using mean values unless otherwise specified (Tables 1, 2, 3, 4). The risk of bias of selected studies was highly variable (Supplementary 2).

HUMAN STUDIES

A. Electrolytes

a. Dietary Sodium

In 4 human studies, participants were administered a sodium-controlled diet for a period of 1 to 3 weeks (21–24). Three studies enrolled healthy subjects and reported no difference in UV between a high vs. normal or low-salt diet (21–23). One study enrolled patients with hypertension and reported a significant increase in UV in the high-salt diet (UV: 2046.3 mL/24-h) compared to the low-salt diet

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(1751.6 mL/24-h) in subjects with the highest UNa^+ excretion tercile (24). UNa^+ excretion was significantly different between groups in all 4 studies.

Four others studies reported the effect of salt intake on UV (25–28). In healthy women, a 24% increase in UV (30 vs 37.8 ml/kg/24-h) and a six-fold increase in UNa^+ excretion from low-to-high dietary sodium were observed (26). Similar results were reported in healthy young adults (28), healthy males (25) and untreated hypertensive patients (27).

b. Salted water

One RCT reported a significant reduction in UV with 27 mmol/L and 52 mmol/L sodium drinks compared to 7 mmol/L and 15 mmol/L solutions in healthy men (29). UNa^+ excretion was not reported.

c. Sports drinks

Sports drinks are characterized by a high electrolyte content (30). Two RCTs of healthy men found no significant difference in UV with sports drinks compared to water (30,31).

B. Osmotically active substances

a. Sugars

In a RCT comparing orange juice and cola to still water in men (30), UV was significantly lower following consumption of orange juice vs. still water but not significantly changed with cola.

Another RCT reported a significant decrease in UV in men with 10%- and 20%-sucrose drinks compared to water, whereas no effect was observe with 5% sucrose drink (29). UNa^+ excretion was not reported.

b. Sugar substitutes/sweeteners

Diet cola (30) and saccharin-sweetened water (32) intake showed similar UV (30,32), UNa^+ (30), and UK^+ (30) excretion patterns to still water in humans.

c. Alcohol

Consumption of wine and spirits by older men led to a significant increase of UV and decrease of UNa^+ and UK^+ excretion compared to their non-alcoholic drinks (33). Beer showed no difference in UV (30,33) compared to non-alcoholic beer (33) or to water (30). Total UV upon ingestion of alcoholic beer and non-alcoholic beer was significantly higher than for all other alcoholic and their non-alcoholic drinks (33). Sequential consumption of beer followed by water compared to water alone had no significant effect on UV, UNa^+, or UK^+ (34).

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d. Meat

A non-RCT enrolled healthy males who consumed an average 3.5 g/kg body weight of lean cooked beef steak on the test day and an amount of sodium and water equivalent to the steak on the control day (35). Compared to the control, UNa^+ and UK^+ excretion increased significantly during the 3 hours following the protein load. Urinary flow rate (4.6 ml/min) didn't increase compared to the control (6.1 ml/min) (35).

C. Milk and milk-based drinks

Two RCTs reported a decrease in UV in men who ingested milk versus water. In the first study, UV was significantly reduced with full-fat (1052 g/4h) and skim (1049 g/4h) milk compared to still water (1337 g/4h) (30). In the second study, significantly decreased UV was noted after ingesting skim milk (794 mL/5h) versus water (1429 mL/5h) (31).

The consumption of yoghurt drinks by men did not significantly affect UV but did significantly increase UNa^+, UK^+ and UCl^- excretion (36).

D. Caffeinated drinks

a. Coffee

A RCT demonstrated an increase in UNa^+ excretion among men who consumed caffeinated coffee compared to decaffeinated coffee, but had no impact on UV (37). However, ingestion of caffeinated coffee significantly increased UV (215 ml/h to 362 ml/h) and UNa^+ and UK^+ compared to baseline values (37). Two other crossover studies involving men reported similar results (30,38).

In two crossover studies (39,40), significantly greater UV, UNa^+ and UK^+ were reported in adults with high-caffeine coffee compared to water and low-caffeine coffee. No significant effects on UV, UNa^+ or UK^+ were observed with low-caffeine coffee compared to water (39). The second study reported significantly increased UV following caffeinated coffee intake compared to baseline values (40).

b. Tea

No significant difference in UV was observed between men drinking tea compared to water (30).

c. Energy drinks

Energy drinks generally contain high amount of caffeine (41). Significantly greater UV and UNa^+ were observed with consumption of energy drinks compared to placebo (UV: +243 ml/6-h, 95%CI [115-372]) (41).

d. Caffeinated water

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A RCT comparing ingestion of caffeinated water volume at various concentrations (up to 400 mg/L) (29) reported no significant difference in UV, compared to non-caffeinated water.

ANIMAL STUDIES

A. Sports drinks

A single animal study identified no significant effect on UV, UNa^+ or UK^+ when rats ingested sports drinks compared to water (42).

B. Milk and milk-based drinks

In rodent models, oral administration of full-fat milk decreased UV and increased UNa^+ and UK^+ excretion (42), whereas a milk protein solution reduced UV with no change in UNa^+ and UK^+ excretion (42), and a milk electrolyte solution increased UNa^+ and UK^+ excretion with no significant change in UV (42).

C. Fruits

a. Prickly pear

Infusions of cladode, flower, and fruit significantly increased total 24-hour UV (38.2, 32.4 and 39.0 mL, respectively) compared to the controls (24.2 mL) (43). No significant effect was observed on UNa^+ and UK^+ excretion.

b. Grangel

Aqueous fruit extract at 20, 40 and 60 mg/kg significantly increased 24-hour UV (9.86, 12.02, and 13.48 mL/24-h, respectively) compared to the control (4.97 mL/24 hours) (44).

c. Wild raspberry

Methanol extract significantly increased UV (2.32 mL/100 g) compared to controls (1.3 mL/100 g) (12). In addition, wild raspberry extract significantly reduced the UK^+ excretion and increased UNa^+ excretion. UV, UNa^+, UK^+ excretion with raspberry aqueous extract were similar to controls (12).

d. Goji berries

Oral administration of 250 and 500 mg/kg goji berry powder, significantly increased UV (8.08 and 10.05 ml/100gm/24h respectively) in a dose-dependent manner (13). UNa^+ and UCl^- excretion were significantly increased compared to controls. A significant decrease in UK^+ excretion was observed compared to controls.

e. Bijaura fruit

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Oral administration of fruit juice significantly increased UV (22.17 mL) compared to controls (16.83 mL) (45).

D. Vegetables

a. Roselle

Aqueous extracts dosed at 1500, 2000, and 2500 mg/kg significantly increased UV (3.0, 4.3, and 4.4 ml/h, respectively) compared to baseline (1.0 ml/h). UNa^+ also significantly increased in a dose-dependent manner whereas UK^+ excretion was unchanged (46).

b. Amaranth

Amaranth aqueous extracts showed no significant effect on UV (14). Conversely, UNa^+, UK^+, and UCl^- excretion were significantly increased with 500 mg/kg dosing as compared to controls.

c. Nasturtium

Compared to controls, UV and UNa^+ excretion significantly increased with ethanolic extract. No significant effect was observed in UK^+ excretion (47).

d. Moringa

Moringa leaf aqueous and hot tea extracts significantly increased UV, UNa^+, UK^+, and UCl^- excretion compared to the control group (15).

e. Wild mushroom

All doses of wild mushroom extract significantly increased UV at 6- and 24-hour intervals as compared to the control group (48). Twenty-four-hour UNa^+, UK^+, and UCl^- excretion were also significantly higher at all-time points compared to the control group. Long-term doses of 250 and 500 mg/kg significantly increased 24-hour UV (24.75 and 28.67 ml, respectively) compared to controls (22.5 ml). UNa+, UK^+, and UCl^- were also significantly increased by all doses (48).

f. Black radish

Ingestion of aqueous extracts significantly increased 24-h UV (6.24 to 9.93 mL) in a dose-dependent manner (49).

g. Sorrel

Ethanol extracts dosed at 750 and 1000 mg/kg significantly increased UV (3.5 and 4.2 mL, respectively) compared to controls (16). Significant increases in the excretion of UNa^+, UK^+ and UCl^- was observed with ethanol extracts in a dose-dependent manner.

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h. Kidney leaf morning glory

Aqueous extract dosed at 600 mg/kg significantly increased UV (2.61 mL/5 hours) and UNa^+ and UK^+ excretion compared to controls (UV: 1.55 mL/5 hours) (50).

E. Herbs and spices

a. Cardamom

Crude extract at doses of 1, 3 and 10 mg/kg significantly increased UV (4.1, 5.0, 5.5 ml/100g/6h respectively) compared to the control group (3.4 ml). UNa^+ and UK^+ excretion were also significantly increased at these doses compared to the control group (51).

b. Parsley

Two studies have reported increased UV after ingestion of parsley extract. In the first study, 24-hour UV was significantly increased compared to placebo (12.8 vs 10.9 ml) (52). Similar results were reported in the second study (53).

c. Rosemary

Aqueous extract (8%) significantly increased 24-hour UV from study day 5 onwards. UNa^+ excretion was increased on the first study day and then again from the fifth study day onwards compared to controls (54). UK^+ excretion was significantly increased across the study period except for a single day. Sixteen percent aqueous extract significantly reduced UV, UNa^+, and UK^+ on study day 1, while significant increases in UNa^+ and UK^+ were noted at later time points (54).

d. Aniseed oil

A significant anti-diuretic effect was observed with aniseed oil mixed with drinking water compared to controls (urine-to-water intake ratio 27.7 versus 47.36), with no significant effect on water intake compared to controls (35.94 versus 33.78 ml) (55).

e. Black cumin

Oral administration of black cumin significantly increased UV (14.59 ml/kg/24h) compared to controls (9.54 ml/kg/24h) (17). No significant effect on UNa^+ and UK^+ was observed (17).

f. Caraway

Aqueous extracts significantly increased UV, starting from study hour four until the 24-hour time point (5.7 and 12.8 ml, respectively) compared to controls (3 and 7.7 ml, respectively) (56). Twenty-four-hour UNa^+ and UK^+ excretion were significantly higher in the caraway group compared to the

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control group and reference (furosemide) group (56). Chronic administration significantly increased UV from study day 1 through study day 6 (9.3 ml to 20.2 ml) versus controls (5.4 ml to 5.8 ml). UNa^+ excretion significantly increased from study day 4 through study day 8 (56).

g. Garlic

N-butanol fractions of fresh garlic bulbs rendered a dose-dependent diuretic effect (9.3 mL/5h) compared to controls (5.5 mL/5h) (57). UNa^+ excretion was significantly increased compared to controls.

h. Saffron

Aqueous extracts significantly increased UV (from 18.63 to 28.39 mL/5h) compared to controls (8.23 mL/5h) (58). At the highest dose, UNa^+ excretion was significantly increased compared to controls and the reference (hydrochlorothiazide) group. UK^+ excretion was significantly decreased with the lowest dose, but increased at the highest dose compared to controls.

i. Java tea

Aqueous extracts significantly increased UV in a dose-dependent manner (7.87-16.60 ml/kg/4h) compared to controls (1.07 ml/kg/4h)(59). UNa^+ was not significantly affected and UK^+ excretion significantly increased (59). Single-dose methanol extracts significantly increased UNa^+ and UK^+ excretion without affecting UV (60). Chronic ingestion significantly increased UV beginning on study day 3; UNa^+ excretion beginning on study day 4; and UK^+ excretion starting on study day 2 (60).

d. Honey

In animal studies, honey administration significantly increased the UV (11,61,62), UNa^+ (11,62), UK^+ (62), and UCl^- (11) excretion.

DISCUSSION

Summary of evidence

High dietary sodium, as well as wine, spirits, and high-caffeine coffee, caffeinated energy drinks, increased UV in human studies. Conversely, decreased UV was associated with low dietary sodium and consumption of milk, orange juice, and high-salt/high-sugar drinks. Cola, diet cola, sports drinks, yoghurt drinks, and tea had a diuretic effect similar to that of water. Consuming meat meal (beef) compared to an equivalent amount of sodium and water, significantly increased urinary sodium excretion, but not urine flow in healthy men. In animal studies, a variety of fruits, vegetables, herbs, spices, and honey were associated with increased UV, whereas aniseed oil decreased UV.

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Explanatory Hypotheses

UV is predicated on a complex interplay between dietary water, solute load, and renal handling of these substances in response to a wide variety of diverse neuroendocrine inputs (Supplementary 3).

Food composition, especially macronutrient load and electrolyte concentration, influence the rate of gastric emptying, and the digestion, and intestinal absorption of nutrients, and thus may indirectly affect UV and fluid homeostasis (29). Dietary food is the predominant source of electrolytes and other osmotically active substances which are central to renal free water and solute handling and thus directly mediate UV (4,63–65). Moreover, UV may also be influenced by dietary protein intake, via the well-described processes of glomerular hyper-filtration and natriuresis which occur following a large dietary protein load (35,64,66) (and thought to be mediated by variations in post-prandial vasopressin, glucagon, prostaglandins, nitric oxide, dopamine, and the renin-angiotensin system axis) (64,66). The diuretic effects of alcohol are thought to be due to the suppression of vasopressin by ethanol (34,67). Caffeine is believed to induce diuresis and natriuresis through a reduction in fractional sodium reabsorption at the proximal tubules (39) and distal nephron (29). Bioactive phytochemicals may be associated with a broad range of physiologic mechanisms, including flavonoids and caffeic acid derivatives in java tea extracts (60), upregulation of the on Na^+-K^+ ATPase by aniseed oil (55), or rather inhibition of the Na^+-K^+ ATPase by parsley and garlic (52,68).

Importance and Limitations

The selected studies were collectively characterized by significant heterogeneity—particularly in study design and primary outcomes—which precluded a quantitative analysis. The majority of included studies were performed on otherwise healthy adult males yet UV may be influenced by inter-individual differences in nutritional and hydration status, physical activity, dietary habits, renal function, and systemic comorbidities. Thus, findings may not be completely generalizable to other populations—particularly those with a high burden of comorbid conditions. The present study was limited to select the articles published in English language. Despite these limitations, the present analysis was the first systematic review to evaluate the effect of specific foods, food constituents, and drinks on UV. The risk of bias across selected studies was evaluated using standardized instruments in order to facilitate transparent appraisal of the available data. Furthermore, excess urine production is not simply a urological disorder, but rather a complex and multifactorial condition, and may be the presenting symptom of a wide range of hypervolemic states and other serious systemic conditions. Accordingly, we believe that our article will be of interest to a diverse readership.

Implementation and Future research

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The of literature, amassed through the search process, includes a diverse array of human and clinically relevant animal studies which may provide the foundation for future human studies research and more refined guidelines for the role of specific foods and drinks in the management of polyuria.

A growing body of evidence, including several animal studies reported in the present systematic review, has refined and extended the concept of a *diuretic index* to more objectively appraise diuretic activity (11–17). Specifically, the *diuretic index* is defined as ratio of urine excretion in a test group to a control group, wherein substances with a *diuretic index* >1.5, between 1-1.5, 0.72-1, and <0.72 have been described as having "good," "moderate," "mild," and "minimal/absent" diuretic activity, respectively (15). Based on this assessment, food items such as wild raspberry (12), goji berries (13), moringa (15), black cumin (17), and Tulkarm honey (11) have shown good diuretic activity in animal studies. Importantly, recent research suggests that a similar measure, the "beverage hydration index", may be valid when used in research involving human subjects (30). Analogous to the *glycaemic index* used to characterize blood glucose response to specific foods (wherein pure glucose is used to as a reference values) (69), a *diuretic Index* may potentially be incorporated in food composition databases, and thus directly contribute to dietary counselling for polyuria and other disorders of volume homeostasis (Figure 2).

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CONCLUSION

The present study provides is a state-of-the-art review on the scientific evidence of the role of food and nutrients on UV. Current evidence suggests that several types of food and drinks may impact body fluid metabolism but the quality of these data is variable. Urine production appears to be influenced by multiple factors including composition (i.e., water, macronutrients, and electrolytes), metabolite load, and the presence of specific diuresis-promoting substances (e.g., caffeine and alcohol) and other bioactive phytochemicals. Future research is needed to confirm current evidence and further explore the physiologic mechanisms underlying these findings.

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LIST OF TABLES AND FIGURES

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Table 1. Effect of Electrolytes on Urine Volume, Urinary Sodium, And Potassium Excretion

Study	Study design	Population	Dose	Order	Duration per diet/dose	UV	UNa^+	UK^+
SALT								
HUMAN STUDIES								
Maughan et al. 2019	CO/R/DB/CT	12 euhydrated and fasted healthy males Age: 25 ±4 years BMI: 24.6 ±2.2 kg/m^2	Salted water: 15 mmol/L 27 mmol/L 52 mmol/L	Random	4 hours	0 ↙ ↙	- - -	- - -
Heyne N et al. 2004	CO/R/CT	12 normotensive healthy adults M/F: 6/6 Age (median): 25.5 years BMI: 23.9 ±0.9 kg/m^2	Dietary salt Low: <5 g/day High: Normal + 100 mg/kg/day	Random	8 days	0 0	↙ ↗	↗ 0
Palacios C et al. 2004	CO/R/CT	22 black girls Age: 12.4 ± 0.3 years 14 white girls Age: 13.2 ±0.3 years	Dietary salt Low: 1.3 g/d High: 4 g/d	Random	3 weeks	0 0	↙ ↗	- -
Cuzzola et al. 2001	CO/R/CT/DB	55 adults with mild essential hypertension M/F: 41/14 Age: 47.0 ± 9.9 years	Dietary salt Low: 50 mmol/day High: 150 mmol/day	Random	2 weeks	- ↗(Only in highest salt-	- ↗, (Only in highest salt excreting	-

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		BMI: 26.1±2.4 kg/m²				excreting patients)	patients)	
Luippold et al. 2000	CO/R/CT	10 healthy volunteers Age: 24.9±0.8 years Weight: 75.5±3.3 kg	Dietary salt Normal Low: <5g/day High: Normal+100 mg/kg per day	Random	7 days	- 0 0	- ↙ ↗	- - -
He FJ et al. 2001	CO/CT	104 adults with essential hypertension M/F: 48 (33 white, 15 black) /56 (38 white, 18 black) Age: 48 years	Dietary salt High: 350 mmol/day Low: 10-20 mmol/day	High to Low	5 days	↙	↙	↙
Yatabe et al. 2017	CO/CT	14 healthy adults M/F: 5/9 Age: 22.5 ± 0.3 years BMI: 20.4 ± 2.0 kg/m²	Dietary salt Low: 51 mmol/day High: 342 mmol/day	Low to high	7 days	0 ↗	↙ ↗	0 0
Rakova N et al. 2017	CO/CT	10 healthy males Age and BMI: NR	Dietary salt 12 g/d 9 g/d 6 g/d	Low to High	29 days	↗	↗	-
Anderson et al. 2008	CO/CT	28 healthy normotensive Caucasian females	Dietary salt Low: 0.7	Low to High	6 days	↗	↗	-

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		Age: 53 ± 1.6 years BMI: 25.2 ± 0.6 kg/m²	mmol/kg/day High: 4 mmol/kg/day					
SPORTS DRINKS								
HUMAN STUDIES								
Maughan et al. 2016	CO/R/CT	17* euhydrated and fasted males Age: 24 ±4 years Weight: 77.3 ±9.9 kg	Sports drink: 1 L (Na: 21 mmol/L, K: 4 mmol/L)	Random	4 hours	0	↙	↗
Seery et al. 2016	CO/R/CT	7 healthy males Age: 26 ±6 years, Weight: 86.4 ±11.5 kg	Sports drink (Na: 21 mmol/L, K: 4 mmol/L): 2.8 ± .56 L	Random	5 hours	0	-	-
ANIMAL STUDIES								
Ishihara et al. 2013	CT	18* male Wistar rats Age (mean): 8 weeks Weight (range): 200–250 g	Sports drink (Na: 19.5 mmol/L, K: 5 mmol/L): 6 ml	-	4 hours	0	0	0

CO: crossover, R: randomized, CT: control SB: single-blinded, DB: double-blinded, M/F: male/female, BMI: Body mass index, UV: urinary volume, UNa^+: urinary sodium, UK^+: urinary potassium, - : not reported, 0: no significant effect, ↗: significant increase, ↙: significant decrease, *: number of subjects/animals per test group. Data are reported as mean ± standard deviation unless otherwise specified.

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Table 2. Effect of Osmotically Active Substances on Urine Volume, Urinary Sodium, And Potassium Excretion

Study	Study design	Population	Dose	Duration per diet/dose	Washout period	UV	UNa^+	UK^+
MEAT								
HUMAN STUDIES								
Hostetter T, 1986	CO/CT	10 healthy adults M/F: 6/4 Age (average [range]): 23 [20-27] years	Lean cooked beef steak: 3.5 g/kg	3 hours	1 day ≤	0	↗	↗
SUGARS								
HUMAN STUDIES								
Maughan et al. 2016	CO/R/CT	17* euhydrated and fasted healthy males Age: 24 ±4 years Weight: 77.3 ±9.9 kg	Orange juice (sugar 10.5 g/100 mL): 1 L Cola (sugar 10.6 g/100 mL): 1 L	4 hours	-	↙ 0	0 0	↙ ↗
Maughan et al. 2019	CO/R/DB/CT	12* euhydrated and fasted healthy males Age: 26 ±6 years BMI: 23.9 ±2.7 kg/m^2	Sucrose: 50 g/L 100 g/L 200 g/L	4 hours	7 days	 0 0 ↙	 - - -	 - - -
HONEY								

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ANIMAL STUDIES								
El-Haskoury et al. 2015	R/CT	5 adult male Wistar rats Weight (range): 230–278 g	Carob honey: 100 mg/kg	24 hours	-	↗	↗	↗
				9 days	-	↗	↗	↗
Imtara et al. 2018	R/CT	6 Wistar rats Weight (range): 200–240 g	Tulkarm honey: 100 mg/kg	24 hours	-	↗	↗	0
				11 days	-	↗	↗	0
El-Guendouz et al. 2017	CT	6 male Wistar rats Weight: 190 ± 40 g	*Capparis spinose* honey: 1000 mg/kg	21 days	-	↗	0	0
SWEETENERS								
HUMAN STUDIES								
Bakali et al. 2017	CO/R/SB/CT	40 healthy women (Indian Asian 20, Caucasian 20) Age (range): 20-50 years	Saccharin 5 mg/kg	2 hours	28 days	0	-	-
Maughan et al. 2016	CO/R/CT	16* euhydrated and fasted males Age: 24 ±4 years Weight: 77.3 ±9.9 kg	Diet cola (aspartame 180 mg/354 mL): 1 L	4 hours	-	0	0	0
ALCOHOL								
HUMAN STUDIES								
Jiménez-Pavón et al. 2015	CO/R/CT	16 physically active, healthy males Age: 21.1 ± 1.4 years	Beer (1.8 % alcohol): 660 ml	2 hours	3 weeks	0	0	0

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		Weight: 74.1 ± 6.5 kg						
Polhuis et al. 2017	CO/R/CT	20 males Age (median [range]): 69 [65-75] years Weight: 77.7±9.9 kg	30g of alcohol: Beer (5% alcohol) wine (13.5% alcohol) spirits (35% alcohol)	4 hours	7 days	- 0 ↗ ↗	- 0 ↙ ↙	- 0 ↙ ↙
Maughan et al. 2016	CO/R/CT	17* euhydrated and fasted males Age: 24 ±4 years Weight: 77.3 ±9.9 kg	Beer (4% alcohol): 1 L	4 hours	-	0	↗	↗

CO: crossover, R: randomized, CT: control/placebo SB: single blinded, DB: double blinded, M/F: male/female, BMI: body mass index, UV: urinary volume, UNa^+: urinary sodium, UK^+: urinary potassium, - : not reported, 0: no significant effect, ↗: significant increase, ↙: significant decrease, *: number of subjects/animals per test group. Unless otherwise specified, the data are expressed as mean± standard deviation.

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Table 3. Effect of Caffeinated and Non-caffeinated Drinks On Urine Volume, Urinary Sodium And Potassium Excretion

Study	Study design	Population	Dose	Order	Duration per diet/dose	UV	UNa^+	UK^+
CAFFEINATED DRINKS: COFFEE								
HUMAN STUDIES								
Nussberger et al. 1990	CO/R/SB/CT	8 healthy males Age (range): 24-28 years	Coffee: 250 mg caffeine	Random	3 hours	0	↗	0
Killer et al. 2014	CO/CT	50 healthy males Age: 28.1 ±7.3 years Weight: 77.0 ± 12.1 kg	Coffee: caffeine 4 mg/kg	Random	3 days	0	↗	-
Maughan et al. 2016	CO/R/CT	17* euhydrated and fasted males Age: 24 ±4 years Weight: 77.3 ±9.9 kg	Coffee: caffeine 212 mg/L	Random	4 hours	0	↗	0
Seal et al. 2017	CO/SB/CT	10 healthy adults M/F: 8/2 Age: 27 ± 5 years BMI 29.1 ± 4.4 kg/m²	Coffee: low caffeine 3 mg/kg high caffeine 6 mg/kg	Low to High	3 hours	0 ↗	0 ↗	0 ↗
Peerapen et al. 2017	CO/CT	30 healthy adults M/F: 7/23 Weight: 58.0 ± 14.9 kg	Coffee: 2.75 ± 0.54 mg caffeine/kg	-	3 hours	↗	-	-

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CAFFEINATED DRINKS: OTHERS								
HUMAN STUDIES								
Riesenhuber et al. 2006	CO/SB/CT/R	12 healthy males Age (median[range]): 25 [18–28] years	Energy Drinks: 240 mg caffeine	Random	6 hours	↗	↗	-
Maughan et al. 2016	CO/R/CT	15* euhydrated and fasted males Age, weight: cf. Table 1	Hot tea: caffine179 mg/L Cold tea: caffeine 179 mg/L	Random	4 hours	0 0	↗ 0	0 0
Maughan et al. 2019	CO/R/DB/CT	12 euhydrated and fasted healthy males Age: 25 ±4 years BMI: 24.6 ±2.2 kg/m^2	Caffeine: 50 mg/L 200 mg/L 400 mg/L	Random	4 hours	0 0 0	- - -	- - -
NON-CAFFEINATED DRINKS: MILK/MILK BASED DRINKS								
HUMAN STUDIES								
Maughan et al. 2016	CO/R/CT	17* euhydrated and fasted males Age: 24 ±4 years Weight: 77.3 ±9.9 kg	Full fat milk: 1 L Skimmed milk: 1 L	Random	4 hours	↙ ↙	↗ ↗	↙ ↙
Seery et al. 2016	CO/R/CT	7 healthy males Age: 26 ±6 years, Weight: 86.4 ±11.5 kg	Skimmed milk: 2.7 L ± 0.426	Random	5 hours	↙	-	-

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Niksefat et al. 2019	CO/R/CT	10 healthy male athletes Age: 21.6 ±0.8 years BMI: 23.16 ±2.84 kg/m^2	Yoghurt drink: 2% BW	-	3 hours	0	↗	↗
ANIMAL STUDIES								
Ishihara et al. 2013	CT	14* male Wistar rats Age (mean): 8 weeks Weight (range): 200–250 g	6 mL: Full fat milk Milk protein solution Milk electrolyte solution	-	4 hours	 ↙ ↙ 0	 ↗ 0 ↗	 ↗ 0 ↗

CO: crossover, R: randomized, CT: control/placebo SB: single blinded, DB: double blinded, BW: body weight, M/F: male/female, BMI: body mass index, - : not reported, UV: urinary volume, UNa^+: urinary sodium, UK^+: urinary potassium, 0: no significant effect, ↗: significant increase, ↙:significant decrease, *: number of subjects/animals per test group. Unless otherwise specified, the data are expressed as mean± standard deviation.

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Table 4. Effect of Herbs, Vegetables and Fruits on Urine Volume, Urinary Sodium, Potassium and Chloride Excretion

Common name/ Species	Study	Study design	Population	Dose	Duration per diet/dose	UV	UNa^+	UK^+	UCl^-
HERBS/SPICES									
ANIMAL STUDIES									
Parsley *Petroselinum crispum/ sativum*	Kreydiyyeh et al. 2002	CT	6 male Sprague-Dawley rats Weight (range): 150–200 g	Aqueous extract: 20 g/100 ml	24 hours	↗	-	-	-
	Vranješ et al. 2016	R/CT	10 Mus musculus albino rats age <3 months Weight (range): 31–46 g	5% aqueous extract	28 days	↗	↗	↗	-
Cardamom *Elettaria cardamomum*	Gilani et al. 2007	R/CT	5 Sprague–Dawley rats Weight (range): 200–220 g Swiss albino mice Weight (range): 20–25 g	Crude extract 1 mg/kg 3 mg/kg 10 mg/kg	6 hours	↗ ↗ ↗	↗ ↗ ↗	↗ ↗ ↗	- - -
Aniseed oil *Pimpinella anisum*	Kreydiyyeh et al. 2003	CT	5 male Sprague-Dawley rats Weight (range): 150–200 g	0.5 ml oil/L	24 hours	↙	-	-	-
Java tea *Orthosiphon stamineus*	Adam at al. 2009	CT	4 male Sprague-Dawley rats Weight (range):180–200 g	Aqueous extract: 5 mg/kg 10 mg/kg	4 hours	↗ ↗	0 0	↗ ↗	0 0

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	Arafat et al. 2008	R/CT	9-10 male Sprague–Dawley rats Weight (range):150–250 g	Methanol extract: 2 g/kg Methanol & water extract (1:1): 2 g/kg	24 hours	0 0	↗ ↗	↗ ↗	- -
			8 male Sprague–Dawley rats Weight (range):150–250 g	Methanol extract: 0.5 g/kg Methanol & water extract (1:1): 0.5 g/kg	7 days	↗ ↗	0 ↗	0 ↗	- -
Rosemary *Rosmarinus officinalis*	Haloui et al. 2000	R/CT	5 male Wistar rats Weight (range): 280– 300 g.	10 ml/kg: 8% aqueous extract 16% aqueous extract	7 days	 ↗ 0	 ↗ ↗	 ↗ 0	 - -
Black cumin *Nigella sativa*	Toma et al. 2015	CT	6 Wistar Bratislava male rats Weight (mean): 200 g	Ethanolic extract: 100 mg/kg	24 hours	↗	0	0	-
Caraway *Carum carvi*	Lahlou et al. 2007	CT	5 male Wistar rats Weight (range):150-200 g	Aqueous extract: 100 mg/kg	24 hours 8 days	↗ ↗	↗ ↗	↗ 0	- -
Garlic *Allium sativum*	Tiwari et al. 2012	R/CT	6 Wistar albino rats Weight (range): 150-200 g	N-butanol fraction: 10 mg/kg 20 mg/kg	5 hours	 0 ↗	 0 ↗	 0 0	 0 0
Saffron *Crocus sativus* stigma	Shariatifar et al. 2014	R/CT	8 male rats Weight (range): 200-220 g	Aqueous extract: 60 mg/kg 120 mg/kg	5 hours	 ↗ ↗	 0 ↗	 ↙ 0	 - -

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				240 mg/kg		↗	↗	↗	-
VEGETABLES									
ANIMAL STUDIES									
Moringa	Fekadu et al.	R/CT	5 male Wistar rats	Aqueous extract:	5 hours				
Moringa	2017		Age (range): 4–6 weeks	62.5 mg/kg		↗	↗	0	0
stenopetala			Weight (range): 200–250 g	125 mg/kg		↗	↗	0	↗
				250 mg/kg		↗	↗	0	↗
				500 mg/kg		↗	↗	↗	↗
				Hot tea infusion:					
				1 teaspoons		↗	↗	0	0
				2, teaspoons		↗	↗	0	0
				4 teaspoons		↗	↗	↗	↗
				6 teaspoons		0	↗	↗	↗
Nasturtium	Gasparotto	CT	5 spontaneously	Ethanolic extract:	7 days				
Tropaeolum majus	Junior et al.		hypertensive male rats	300 mg/kg		↗	↗	0	0
	2012		Age (range): 3–4 months						
			Weight (range): 250-300 g						
Amaranth	Amuthan et al.	CT	6 male albino Wistar rats	Aqueous extract:	24 hours				
Amaranthus	2012		Weight (range):150-200 g	200 mg/kg		0	0	0	0
spinosus				500 mg/kg		0	↗	↗	↗
				1000 mg/kg		0	0	0	0

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				1500 mg/kg		0	0	↗	↗
Wild mushroom	Zhang et al.	CT	6 male Sprague–Dawley rats	Aqueous extract:	24 hours				
Polyporus	2010		Weight (range):180-200 g	50 mg/kg		↗	↗	↗	↗
umbellatus				250 mg/kg		↗	↗	↗	↗
				500 mg/kg		↗	↗	↗	↗
				Aqueous extract:	8 days				
				50 mg/kg		0	↗	↗	↗
				250 mg/kg		↗	↗	↗	↗
				500 mg/kg		↗	↗	↗	↗
Roselle	Alarcón-	CT	6 male Albino Sprague–	Aqueous extract:	5 hours				
Hibiscus sabdariffa	Alonso et al.		Dawley Rats	500 mg/kg		0	↗	0	0
	2012		Weight (range):250–280 g	1000 mg/kg		0	↗	0	↗
				1500 mg/kg		↗	↗	0	↗
				2000 mg/kg		↗	↗	0	↗
				2500 mg/kg		↗	↗	0	↗
Black radish	Vargas S. et al.	CT	Male albino rats	Aqueous extract:	24 hours				
Raphanus sativus	1999		Weight (range): 200-250 g	40 mg/kg		↗	-	-	-
				70 mg/kg		↗	-	-	-
				140 mg/kg		↗	-	-	-
Sorrel	Rao et al. 2011	CT	4 male albino rats	Ethanol extract:	6 hours				
Rumex vesicariys			Weight (range): 150-200 g	750 mg/kg		↗	0	↗	0
				1000 mg/kg		↗	↗	↗	↗

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				Benzene extract					
				750 mg/kg		0	↙	0	↗
				1000 mg/kg		0	0	0	↗
Kidney leaf	Angappan et	CT	5 female Wistar albino rats	Aqueous extract:	5 hours				
morning glory	al. 2018		Weight (range): 150-200 g	200 mg/kg		0	0	0	-
Merremia				400 mg/kg		0	0	0	-
emarginata				600 mg/kg		↗	↗	↗	-
FRUITS									
ANIMAL STUDIES									
Prickly pear	Galati et al.	CT	12 male Wistar rats	5 ml/100 g of:	24 hours				
Opuntia ficus indica	2002		Weight (range): 150-200 g	15% cladodes infusion		↗	0	0	-
				15% flowers infusion		↗	0	0	-
				15% fruits infusion		↗	0	0	-
				1.5 ml/100 g of:	7 days				
				15% cladodes infusion		↗	-	-	-
				15% flowers infusion		↗	-	-	-
				15% fruits infusion		↗	-	-	-
Grangel	Vargas Solis et	CT	Male albino rats	Aqueous extract:	24 hours				
Randia echinocarpa	al. 2002		Weight (range): 200-250 g	10 mg/kg		0	-	-	-
				20 mg/kg		↗	-	-	-
				40 mg/kg		↗	-	-	-
				60 mg/kg		↗	-	-	-

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Wild raspberry	Zhang et al.	CT	6 male rats	2 g/kg:	4 hours				
Rubus idaeus	2011		Weight (range): 250-300 g	Aqueous extract		0	0	↙	-
				Methanol extract		↗	↗	↙	-
Goji berries	Pai et al. 2014	CT	6 Wistar albino rats	Fruit powder:	24 hours				
Lycium barbarum			Weight (range): 150-200 g	250mg/kg/day		↗	↗	↙	↗
				500mg/kg/day		↗	↗	↙	↗
Bijaura fruit	Shah et al.	R/CT	6 urolithiasis induced male	Fresh fruit juice:	28 days	↗	-	-	-
Citrus medica	2014		Wistar rats	250 mg/kg					
			Weight (range): 250-300 g						

CO: crossover, R: randomized, CT: control/placebo, UV: urinary volume, UNa^+: urinary sodium, UK^+: urinary potassium, UCl^-: urinary chloride, - : not reported, 0: no significant effect, ↗: significant increase, ↙: significant decrease. The number of animals is mentioned per test group. Test dosages of herbal/spice extracts were mentioned based on their extraction methods as either “aqueous” or “methanol”/“ethanol”. The latter involved extraction of dry ground materials using alcohol-based solvent which was then vacuum evaporated.

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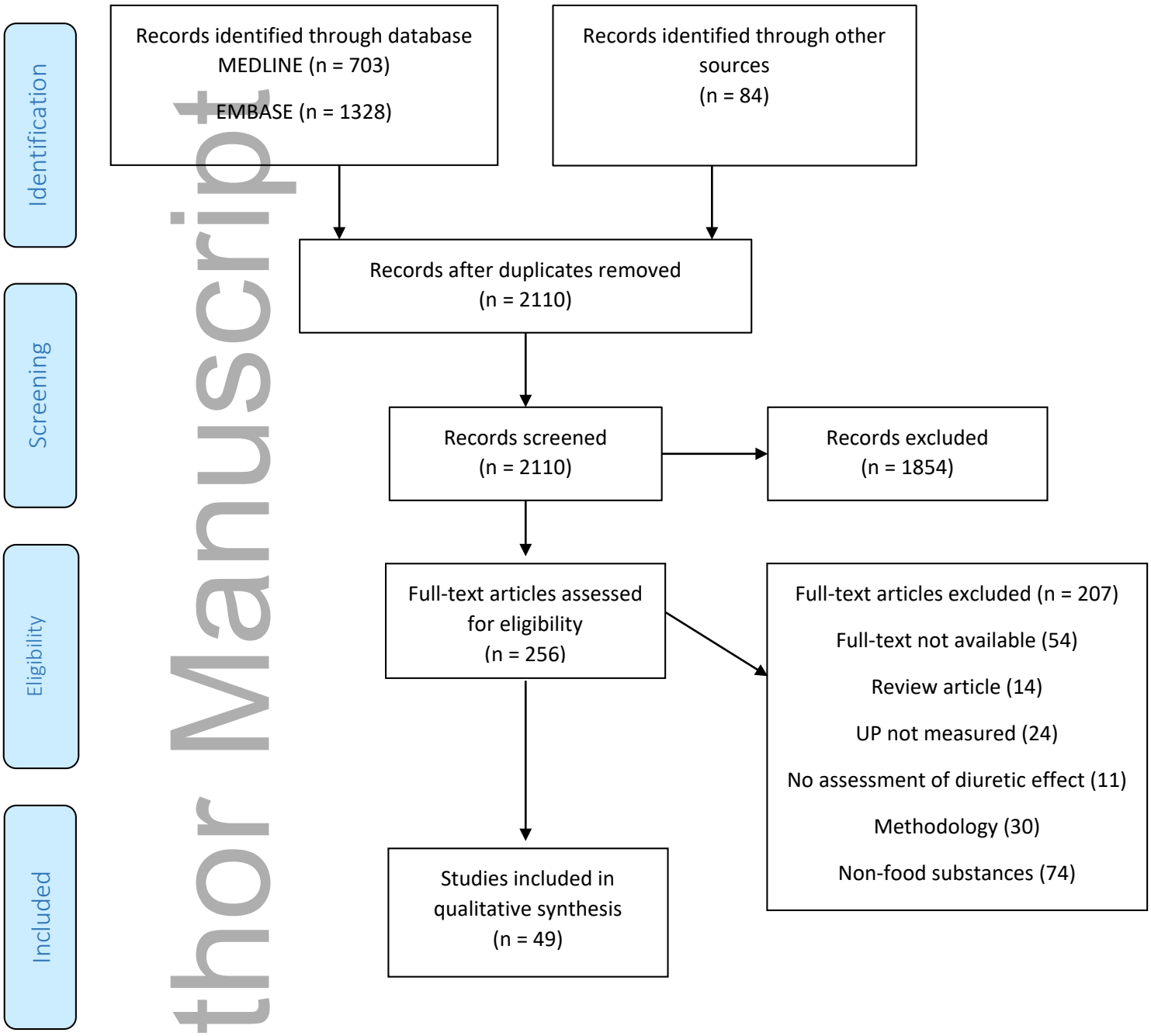
Figure 1: Study Selection Flow Diagram



Note: Abbreviations: UP – Urine Production

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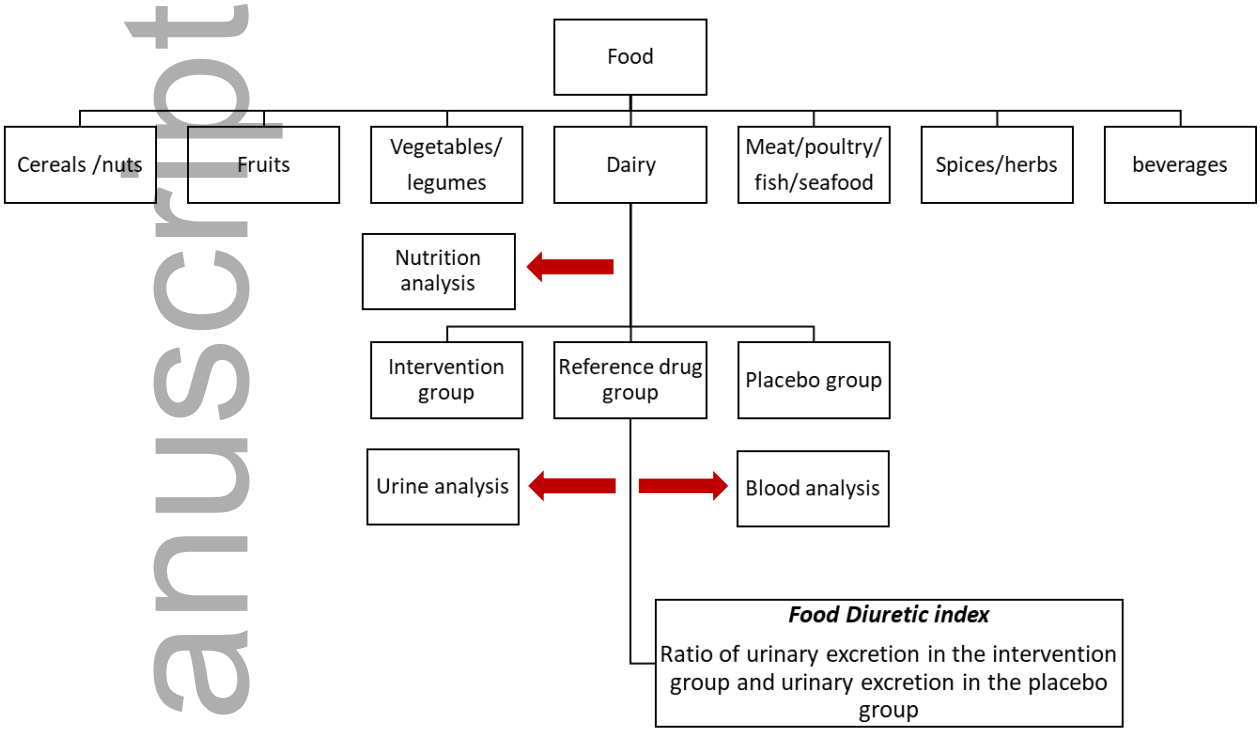
Figure 2: Proposed experimental plan for the development of a Food Diuretic Index



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