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NEPHROPROTECTIVE EFFECT OF LEMONGRASS (*CYMBOPOGON FLEXUOSUS*) AND CELERY (*APIUM GRAVEOLENS*) BASED DETOXIFYING DRINKS AGAINST CARBON TETRACHLORIDE-INDUCED NEPHROTOXICITY IN ALBINO RATS

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ABSTRACT

Indigenous plants such as lemongrass and celery are rich sources of nutrients. There is a need to test their efficacy for ameliorating nephrotoxicity. Plant-derived drugs have emerged as alternative medicine. Previous studies have focused only on the formulation of detoxifying drinks but its *in vivo* studies were not performed. The present research was conducted to formulate and evaluate the nutritional composition and antioxidant potential of detoxifying drink variants and to assess their ameliorative effect on the renal toxicity induced by carbon tetrachloride (CCl_4) at 0.5ml/kg/day i.p in Wistar albino rats. Different detoxifying drink variants were prepared by adding 0.5%, 1.0% and 1.5% of lemongrass powder (LG5, LG10 and LG15) and celery powder (CL5, CL10 and CL15) respectively to the standard drink SD. These additions resulted in a significant increase ($p \leq 0.05$) in all the nutritional parameters. *In vivo* data revealed that CCl_4 induced toxicity by increasing malondialdehyde (MDA) (6.87nmoles/ ml RBC lysate), decreased glutathione concentration (3.44µmole/ml RBC lysate) and attenuated antioxidant enzymes activity (U/mg protein) of SOD (0.82), GPx (5.83) and CAT (1.66). Detoxifying drinks significantly ($p \leq 0.05$) corrected urea, uric acid and creatinine levels in plasma. Group VI and VIII receiving LG15 and CL15 variants of detoxifying drink restored the enzymatic (SOD, GPx and CAT) activity ($p \leq 0.05$) and non-enzymatic parameters (GSH) and attenuated the lipid peroxidation in erythrocyte lysate. The detoxifying drink variant with 1.5% celery powder was equivalent to silymarin (herbal medicine) in protecting the kidney against CCL_4-induced toxicity.

Keywords: Antioxidant potential; celery; carbon tetrachloride; lemongrass; nephrotoxicity

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INTRODUCTION

The kidney is the major organ vulnerable to drug-induced toxicity resulting in acute kidney injury (AKI), chronic kidney disease (CKD), acute renal failure and end-stage renal ailment. Besides hepatotoxicity, drug induced-nephrotoxicity is a frequent problem faced by hospitalized patients due to the unavoidable consumption of nephrotoxic drugs (Khwaja, 2012; Tiong *et al*., 2014). Around 5-7% of hospitalized patients develop AKI due to augmented prescription of drugs, drug-drug interaction and drug-related complications (Wu and Huang, 2018). Glomerulus filtration rapidly removes waste products from the blood. Moreover, renal tubules are accountable for the reabsorption and secretion of substances (Tiong *et al*., 2014; Wu and Huang, 2018). Any dysfunction in the kidney leads to the accumulation of creatinine, urea and other by-products (Tiong *et al*., 2014). The foremost mechanism documented to trigger CKD involves oxidative damage and excessive free radical production. The production of free radicals in the body is due to exposure to environmental pollutants and the action of certain drugs that alter cellular protein structure and attack lipids in the cytoplasmic membrane while depleting the antioxidant defence mechanism (Hijazi and Mouminah, 2017).

Carbon tetrachloride (CCl_4) intoxication in animals is the most widespread experimental model that mimics oxidative stress due to its molecular distinctiveness (Scholten *et al*., 2015). Many studies have demonstrated the nephrotoxic effect of CCl_4. CCl_4 administration causes an increase in the levels of renal function tests such as creatinine and blood urea nitrogen. Moreover, CCl_4-induced inflammation, oxidative stress and apoptosis also cause kidney injury (Hismiogullari *et al*., 2015; Ebaid *et al*., 2021). CCl_4-induced toxicity

begins with the conversion of CCl_4 to trichloromethyl free radical through bioactivation of the cytochrome P450 system. The by-product formed is further degraded to trichloromethyl peroxy and chlorine radicals, aldehyde and phosgene products by covalently binding to microsomal macromolecules like proteins, lipids and nucleic acids (Boll *et al*., 2001; Scholten *et al*., 2015). The further categorical decomposition of peroxidised fatty acids produces by-products like malondialdehyde (MDA), ethane and pentane (Boll *et al*., 2001). An elevated MDA level due to oxidative stress further compromises the GSH levels in the kidney (Ebaid *et al*., 2021).

Plentiful literature proposes that natural products contain free radical–scavenging compounds that can prevent oxidative stress-induced nephrotoxicity (Ademuyiwa *et al*., 2017; Afifah *et al*., 2019). WHO estimates three-quarters of the world currently rely on traditional medicines for therapeutic needs (Danciu *et al*., 2018). Furthermore, to check the cost and frequency of dialysis, drug therapy and kidney transplantation it is imperative to employ traditional medicines to prevent and treat chronic and acute kidney failure (Said *et al*., 2019).

Lemongrass (*Cymbopogon flexuosus*) also known as citronella is a grassy plant with a lemony flavour belonging to *Poaceae* family. India is the largest producer of lemongrass and exports about 80% of its production. It is used in the nutritional, pharmaceutical and flavouring industries (Lonkar *et al*., 2013; Jiang *et al*., 2017). Lemongrass contains several polyphenolic compounds including gallic acid, isoquercetin, quercetin, rutin, catechin and tannic acid which attributes to its high antioxidant activity (Somparn *et al*., 2018). Besides, lemongrass has an abundant reservoir of essential oil like citral, a mixture of geranial and neral; myrcene, citronella, limonene, geraniol, nerol, α-terpineol and eugenol responsible for its distinct flavour and aroma (Lonkar *et al*., 2013; Jiang *et al*., 2017; Li *et al*., 2017). The essential oil and citral in lemongrass are reported to induce phase II drug-metabolizing enzymes like NAD(P)H: quinone oxidoreductase 1 (NQ1), Glutathione-S-transferase (GST) and UDP-glucuronosyltransferase (UGT). It is widely recognized that the induction of phase II enzymes results in a protection against toxicity and chemical carcinogenesis. The findings thus indicate that lemongrass can be used to support detoxification of the body and progress liver health. Besides, the crop also reduces the progression of lipid peroxidation and attenuates the production of ROS in the liver (Li *et al*., 2017). Furthermore, the infusions prepared from dry or fresh leaves of lemongrass are extensively used for the treatments of UTI, hypertension and CVS disorders (Said *et al*., 2019).

Celery (*Apium graveolens*) is an aromatic plant belongs to Apiaceae or Umbelliferae family known as Ajmod in India. Celery has high dietary and medicinal properties among major nutraceutical vegetable species (Golubkina *et al*., 2020; Hijazi and Mouminah, 2017). It is a rich source of dietary fibre, minerals like potassium, manganese, calcium and iron, and vitamins like folate, vitamin B1, B2 and B6 and vitamin A (Golubkina *et al*., 2020). Being a good source of vitamin C, it helps to prevent radical damage that triggers the inflammatory cascade. Celery is abundant in flavonoids, tannin, saponins and steroids while lacking terpenoids. The superior antioxidant activity of celery can be attributed to its high phenolic and flavonoid content (Salem *et al*., 2018). The extract of celery contains polyphenol compounds like chlorogenic acid, caffeic acid, apigenin glucoside, luteolin, apigenin and kaempferol. Among these, apigenin is its main bioactive component (Danciu *et al*., 2018; Afifah *et al*., 2019). Ethnopharmacological studies have revealed that *A. graveolens* has antimicrobial, hepatic and nephroprotective potential and the ability to attenuate oxidative stress (Hijazi and Mouminah, 2017; Tanasawet *et al*., 2017; Salem *et al*., 2018; Afifah *et al*., 2019). Celery aids in the normal and efficient functioning of the kidney by assisting in the removal of body toxins and has been suggested after systematic investigation as a potential herb for the prevention of kidney diseases (Hijazi and Mouminah, 2017).

Blending various food ingredients has proved to be a much more efficient technique to develop nutraceutical products. The synergistic interaction among various constituents in plants enhances its therapeutic potential (Thorat *et al*., 2017).

MATERIALS AND METHODS

Plant material: Cucumber, lemon, apple cider vinegar, cinnamon powder and ginger were procured fresh from the local market. Basil (*Ocimum sanctum*), spearmint (*Mentha spicata*), lemongrass (*Cymbopogon flexuosus*) - Krishna variety and celery (*Apium graveolens*) – Punjab celery 1 were procured from PAU, Ludhiana. Both lemongrass and celery were oven-dried at 45 ˚C for 8 hours and grounded into fine powder.

Detoxifying drink preparation: Plant materials (cucumber, ginger, mint and basil) were blended in different proportions as shown in table 1. The extraction of the drink was done by keeping the beaker in a boiling water bath for 20 minutes. The extract obtained was then strained through a sterile muslin cloth to obtain juice in a container. The final volume was made up to 1L by adding distilled water.

Formulation of Lemongrass and celery detoxification drink variants: Standard drink was used as a baseline to prepare lemongrass and celery variants. The powder was added before boiling the material and the final volume was made upto 1L by adding distilled water. The

lemongrass and celery powder were added at 0.5%, 1.0% and 1.5% for different variants of lemongrass (LG5, LG10 and LG15) and celery (CL5, CL10 and CL15) respectively. Furthermore, each detoxifying drink was concentrated about 2.5 to its original concentration for the animal.

Table 1: Formulations of detoxifying drink variants

Ingredients	SD	LG5	LG10	LG15	CL5	CL10	CL15
Cucumber	200g	200g	200g	200g	200g	200g	200g
Lemon juice	20ml	20ml	20ml	20ml	20ml	20ml	20ml
Ginger sliced	5g	5g	5g	5g	5g	5g	5g
Apple cider vinegar	5ml	5ml	5ml	5ml	5ml	5ml	5ml
Basil leaves	20g	20g	20g	20g	20g	20g	20g
Mint leaves	20g	20g	20g	20g	20g	20g	20g
Cinnamon powder	5g	5g	5g	5g	5g	5g	5g
Lemongrass	-	0.5%	1.0%	1.5%	-	-	-
Celery leaves	-	-	-	-	0.5%	1.0%	1.5%
Final volume made by water	1000ml	1000ml	1000ml	1000ml	1000ml	1000ml	1000ml

SD: Standard drink; LG5: 0.5% of lemongrass powder; LG10: 1% of lemongrass powder; LG15: 1.5% of lemongrass powder; CL5: 0.5% of celery powder; CL10: 1% of celery powder; CL15: 1.5% of celery powder

Nutritional and biochemical evaluation of detoxifying drink variants: The detoxifying drink variants were analyzed for moisture content (AOAC, 2002), mineral content (AOAC, 2002), vitamin C (AOAC, 2002) and β-carotene content (Ranganna, 2002). Total Phenolic Content (TPC) was determined using Folin-Ciocalteu method and expressed as mg GAE/100 ml drink and total flavonoid content (TFC) was estimated by using quercetin as standard and expressing as mg QE/100 ml drink (Mathur and Vijayvergia, 2017). Total Antioxidant Activity (TAA) was analyzed through radical scavenging activity using 2, 2-diphenyl-1-picrylhydrazyl (DPPH) scavenging assay and expressed as % inhibition (Tadhani *et al*., 2007).

Evaluation of organoleptic characteristics: All variants of detoxifying drink were subjected to sensory evaluation by a panel of ten semi-trained panellists from the faculty of Punjab Agricultural University using a nine-point hedonic scale (Wichchukit and O'Mahony, 2015) for various parameters like appearance, color, consistency, aroma, taste and overall acceptability in a controlled environment.

Animal study: Male Wistar albino rats (N= 56, weighing 200-300gm) were procured from the National Institute of Pharmaceutical Education and Research (NIPER), Mohali, Punjab. Rats were caged in plastic cages and were accommodated in a room maintained at standard conditions (22±3 ˚C, 12 h dark/12 h bright). The rats were housed 15 days before the actual start of the experiment to acclimatize to the conditions. The protocol for the study was approved by the Institutional Animal Ethics Committee of the College of Veterinary Science, GADVASU, Ludhiana, India (Approval no. GADVASU/2018/IAEC/46/17). All experiments were carried out following the provided by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India.

The combination of doses selected for feeding rats was based on the highest organoleptic acceptability of the detoxifying drink variants (LG5 and CL5) and the highest nutritional, phytochemical and antioxidant activity that was found in LG15 and CL15 drink variants.

Dosing: The detoxifying drinks variants of 2ml/100g/day were fed orally with the help of a cannula gauge for 4 weeks. Silymarin dissolved in 0.3% sodium CMC was given at 100 mg/kg/day on alternative days for 4 weeks. CCl_4 (solubilized in corn oil in a 1:1 ratio) was given intraperitoneally (i.p) with a 25 gauge needle, 24 hours before sacrificing the animals.

Experimental protocol: The feed and intake of animals was recorded before starting the study and at the end of the experiment.

Group I: (Normal control) rats received only distilled water.

Group II: (Positive control) rats injected with carbon tetrachloride (0.5ml/kg i.p)

Group III: Rats received silymarin (100mg/kg) + CCl_4

Group IV: Rats received standard drink (SD) + CCl_4

Group V: Rats received LG5 + CCl_4

Group VI: Rats received LG15 + CCl_4

Group VII: Rats received CL5 + CCl_4

Group VIII: Rats received CL15 + CCl_4

Sample collection: All rats were sacrificed after 24 hrs of administration of CCl_4 and anaesthetized by light ethyl ether inhalation and sacrificed. Blood was collected through the cardiac puncture into heparinized vials and gently mixed to avoid any clot formation. The heparin tubes were centrifuged at 4˚C at 3000 rpm for 15 min. For further analysis, plasma was removed and stored in an Eppendorf tube at -20˚C. Two ml PBS was again

added to the heparin tubes and centrifuged at 4˚C at 3000 rpm for 15 min. The supernatant was discarded and the procedure was repeated two more times. Cell lysate (25%) was prepared with PBS and used for the estimation of oxidative stress indicators and membrane enzyme activity.

Assessment of renal function indices: Kidney biomarkers in plasma-like urea, uric acid, and creatinine were analyzed using commercial kits (Oscar Medicare). The procedure was followed as mentioned in the kit.

Determination of oxidative stress indices: The supernatant samples obtained from erythrocyte lysate were used for oxidative stress indices. SOD activity was assayed by the method of Madesh and Balsubramaniam (1997) using pyrogallol autoxidation assay. GPx (Glutathione peroxidase) activity was determined by oxidation of GSH in the presence of H_2O_2 as described by Hafeman *et al*. (1974). CAT activity was assayed by the spectrophotometric method as described by Aebi (1983) through H_2O_2 decomposition and total protein by Lowry *et al*. (1951) method using bovine serum albumin (BSA) as a standard. GSH activity was measured by the method of Beutler and Kelly (1963) based on reaction with DTNB. Lipid peroxidation was estimated by assessing malondialdehyde (MDA) by thiobarbituric acid reactive substance assay (Buege and Aust, 1978).

Statistical Analysis: Data from this study was reported as mean±SD for at least three replicates for each sample in product analysis and at least seven replicates for animal study. Data were analysed by JMP Pro 10.0.2 software. One-way analysis of variance (ANOVA) was used for the comparison of means and Tukey-Kramer HSD test was used for posthoc analysis.

RESULTS AND DISCUSSION

Antioxidant Potential of detoxifying drink variants: Table 2 presents the moisture content, vitamin C, β-carotene content, total phenol content (TPC), total flavonoids content (TFC) and total antioxidant activity (TAA) of lemongrass powder, celery powder and their detoxifying drink variants. The moisture content of lemongrass and celery powder was 7.01% and 12.17% respectively. These values are in agreement with previous studies (Duarah and Gupta, 2018; Thorat *et al*., 2017). Moisture content for the standard drink was 99.98 % and the addition of lemongrass powder and celery powder significantly ($p \leq 0.05$) decreased the moisture content.

Celery and lemongrass are rich sources of vitamins especially vitamin C and β-carotene (Caunii *et al*., 2010; Duarah and Gupta, 2018). The antioxidant potential of these micronutrients prevents the progression of lipid peroxidation and protects cellular structures (Lonkar *et al*., 2013; Golubkina *et al*., 2020). In the present study, the vitamin C content of lemongrass powder and celery powder is estimated as 2.12 and 10.13 mg/100g respectively. The vitamin C content of all variants of celery was significantly higher ($p \leq 0.05$) than SD. CL15 had the maximum amount of vitamin C (2.79 mg/100 ml) among all the drink variants. In the case of lemongrass drink variants, only LG15 had significantly higher ($p \leq 0.05$) vitamin C than SD. Duarah and Gupta (2018) have also reported 2 mg/100 g vitamin C content in lemongrass powder. Table 2 shows that β-carotene content is higher in celery powder (2552.66 µg/100g) as compared to lemongrass powder (1921.02 µg/100g). The addition of lemongrass powder and celery powder to standard drink significantly ($p \leq 0.05$) improved the β-carotene content of both lemongrass and celery detoxifying drink variants. CL15 was found to contain maximum beta carotene (132.40 mg/100ml) among all the detoxifying drink variants. The high content of vitamin C and β-carotene in celery leaves has also been reported by Caunii *et al*. (2010).

Table 2: Nutritional and antioxidant potential of detoxifying drink variants

Drink Variants	Moisture (%)	Vitamin C (mg/100ml drink)	β-carotene (µg/100ml drink)	Total Polyphenol Content (mg GAE/100ml drink)	Total Flavonoids Content (mg QE/100ml drink)	Total antioxidant activity (% inhibition of DPPH)
SD	99.48^{a}±0.00	0.34^{a}±0.01	78.27^{a}±0.46	59.15^{a}±0.29	4.48^{a}±0.17	16.46^{a}±0.40
LG5	99.40^{b}±0.05	0.38 ^{ab}±0.01	91.48^{b}±0.20	72.08^{b}±0.96	10.03^{b}±0.63	21.37^{b}±1.27
LG10	99.34^{b}±0.01	0.40 ^{ab}±0.01	103.11^{d}±0.11	81.19^{c}±1.16	15.10^{c}±0.23	30.56^{c}±0.98
LG15	99.22^{c}±0.02	0.43^{b}±0.01	116.10^{e}±0.15	104.75^{e}±5.00	21.86^{d}±0.74	40.76^{e}±1.02
CL5	99.27^{c}±0.01	1.24^{c}±0.01	95.09^{c}±0.23	91.43^{d}±2.73	12.27^{b}±0.36	35.17^{d}±0.95
CL10	99.15^{d}±0.01	1.96^{d}±0.08	118.02^{f}±0.14	120.29^{f}±2.01	20.92^{d}±0.89	48.73^{f}±0.06
CL15	99.00^{e}±0.02	2.79^{e}±0.03	132.40^{g}±0.58	136.48^{g}±3.09	30.20^{e}±1.78	56.81^{g}±1.60

All values represent mean±SD; Values in columns followed by different superscripts differ significantly ($p \leq 0.05$)

Tukey-Kramer HSD has been applied for the given parameters of standard drink and its variants using

celery powder and lemongrass powder

Total Phenol Content (TPC), expressed as mg GAE/100g (dry matter), of lemongrass powder and celery powder, was 2040.20 and 3656.77 respectively. Total Flavonoids Content (TFC), expressed as mg QE/100g (dry matter), of lemongrass powder and celery powder, was 524.63 and 648.91 respectively. TPC and TFC of the standard drink increased significantly ($p \leq 0.05$) with the addition of lemongrass powder and celery leaves powder. CL15 recorded the highest amount of total phenols (136.48 mg GAE) and total flavonoids (30.20 mg QE/100ml drink). The high content of TPC in the various extract of celery has been supported in the literature (Danciu *et al*., 2018; Salem *et al*., 2018). Phenols have a strong antioxidant capacity and potentially prevent the onset of degenerative diseases, especially liver and kidney diseases. Phenols, because of their high molecular weight form a complex with the associated compounds. These complex compounds show high antioxidant activity due to their redox properties which aid in quenching free radicals and damage peroxide (Danciu *et al*., 2018). Flavonoids can change the metabolism of drugs in the human body (Jiang *et al*., 2016). The flavonoids in celery have been shown to increase the antioxidant status and enhance the activity of endogenous antioxidant enzymes (CAT, GPx and SOD) in mice models (Li *et al*., 2014).

DPPH radical scavenging activity expressed in % inhibition of lemongrass powder and celery powder was 71.13% and 97.91%. There was a significant ($p \leq 0.05$) increase in the DPPH free radical capacity of lemongrass and celery detoxifying drink variants as compared to SD. LG15 and CL15 exhibited higher scavenging capacity than LG5 and CL5 respectively. The result revealed that celery has higher TPC and TFC than lemongrass and a subsequent better free radical scavenging capacity. The highest DPPH radical scavenging activity was seen in CL15. Jung *et al*. (2011) studied the antioxidant activity of various extracts of celery and reported that water extract of celery has a substantial amount of scavenging activity (81.44%) as compared to other solvent extracts. This indicates that the aqueous extraction process applied in formulating detoxifying drink extracts retains the major polyphenols and flavonoids in the formulated drink and exhibits high antioxidant activity.

Correlation analysis was used to investigate the interrelationship between TPC, TFC, vitamin C, β-carotene and total antioxidant activity (TAA) of detoxifying drink variants. Table 3 indicates a significant positive correlation between vitamin C and TAA ($r = 0.857$, $p<0.01$), β-carotene and TAA ($r=0.957$, $p<0.01$), TPC and TAA ($r=0.989$, $p<0.01$) and between TFC and TAA ($r=0.951$, $p<0.01$). The results indicate the potential antioxidant activity of the detoxifying drink variants as per the total phenols, total flavonoids, vitamin C and β-carotene present in the crops. The celery leaves and lemongrass crop being rich in phenols and flavonoids provide a good source of antioxidants (Thorat *et al*., 2017; Danciu *et al*., 2018). Flavonoids especially apiin and rutin in celery are reported to contribute to its high antioxidant activity by scavenging free radicals (Li *et al*., 2014). The high antioxidant activity of lemongrass has also been reported in earlier studies (Kusmardiyani *et al*., 2016; Somparn *et al*., 2018). Previous studies have expressed a highly correlated relationship between total polyphenolic content, total flavonoids and antioxidant capacity (Li *et al*., 2014; Kusmardiyani *et al*., 2016; Golubkina *et al*., 2020).

The high correlation shows that phenolic content and flavonoids in both celery and lemongrass contribute to their antioxidant ability which further augments their free radical scavenging capacity. The high antioxidant activity reduces oxidative stress, improves the activity of indigenous antioxidant enzymes and retains GSH levels (Tanasawet *et al*., 2017).

Table 3: Results of Correlation Analysis

Variable 1	Variable 2	Correlation Coefficient (r)
Vitamin C	β-carotene	0.745**
	TPC	0.868**
	TFC	0.748**
	TAA	0.857**
β-carotene	TPC	0.958**
	TFC	0.992**
	TAA	0.957**
TPC	TFC	0.955**
	TAA	0.989**
TFC	TAA	0.951**

**** Significance at 1%,** Total Phenol Content (TPC), Total Flavonoids Content (TFC), Total Antioxidant Activity (TAA)

Organoleptic evaluation of detoxifying drink variants: Fig 1 represents the hedonic score of various attributes of organoleptic characteristics of detoxifying drink variants. LG5 detoxifying drink got significantly ($p \leq 0.05$) highest score in all the parameters like appearance, color, consistency, aroma, taste and overall acceptability compared to other detoxifying drink variants. Among celery variants, CL5 received the significantly ($p \leq 0.05$) highest score in all the parameters. In a study conducted to assess the effect of various drying processes on sensory attributes of lemongrass tea, the color acceptability of lemongrass tea oven-dried at 40˚C was highest. The author suggested that highly volatile compounds present in lemongrass contribute to its distinct flavor and pleasant aroma which increases its overall acceptability in edible products (Mabai *et al*., 2018). In another study, herbal cookies prepared by using 3% of lemongrass powder showed high consumer acceptability (Lonkar *et al*., 2013). This shows the product formulated by using lemongrass has high sensory

acceptance.

The organoleptic attributes of drinks containing a higher concentration of lemongrass and celery (LG15 and CL15) scored less compared to lesser concentrations. This was due to the strong flavor and aroma added by the volatile compounds present in drinks with higher concentrations.

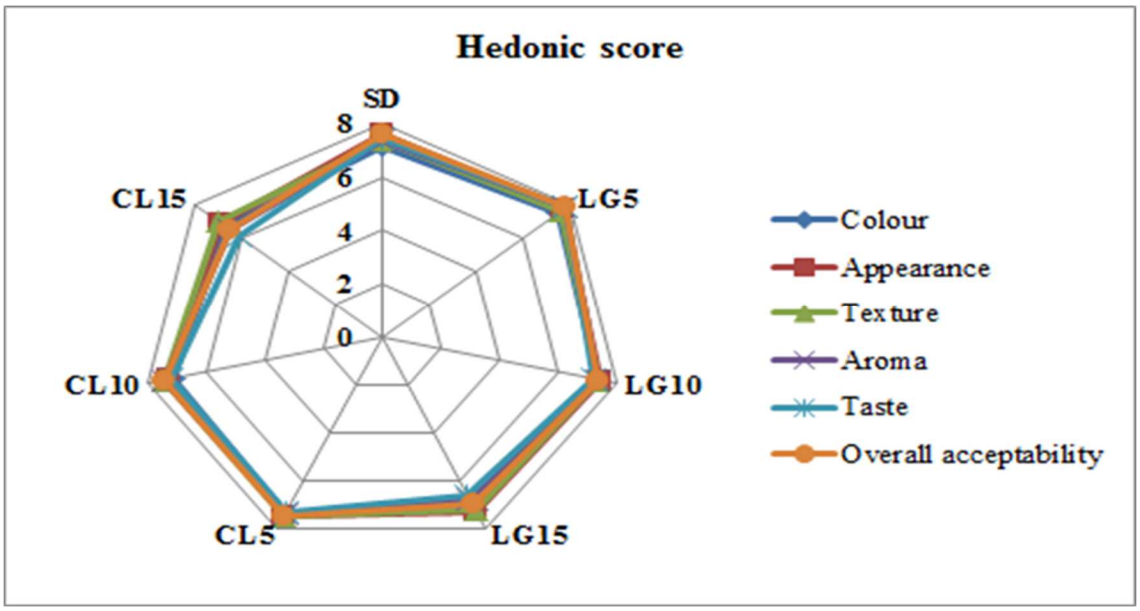

Fig 1. Sensory evaluation of detoxifying drink variants

The mineral content of detoxifying drink variants: Table 4 shows that the addition of lemongrass powder and celery powder to the SD significantly ($p \leq 0.05$) increased the entire mineral content. High calcium and iron contents in lemongrass reported in the present study are in agreement with the results provided by Duarah and Gupta (2018). Celery-based detoxifying drink variants had significantly ($p \leq 0.05$) higher calcium, zinc, selenium, chromium and sodium content as compared to standard drink and lemongrass detoxifying drink variants. Celery-based drinks are rich sources of minerals (Golubkina *et al*., 2020). Iron, magnesium and manganese content were highest in lemongrass variants as compared to celery detoxifying variants at a similar concentration. This can be attributed to the high iron content in lemongrass (Duarah and Gupta, 2018).

The minerals investigated in the study like zinc, manganese, iron, copper and selenium are involved in plant anti-oxidation systems. Though Zn does not participate in redox reactions, its function as an antioxidant is to catalyze the activity of Cu/Zn superoxide dismutase, stabilize the structure of membranes and protect sulfhydryl groups in proteins and regulate the expression of metallothioneins with metal binding capacity (Golubkina *et al*., 2020).

In previous studies, the calcium content and iron content of dried lemongrass were reported to be 200 mg/100g and 22mg/100g respectively (Duarah and Gupta, 2018). In a study by Domagala-Swiatkiewicz and Gastol (2012) the author reported that celery juice is a rich source of magnesium, calcium, iron, zinc, manganese and copper and contains higher macro and micro minerals as compared to carrot juice and red beet juice.

Table 4: Mineral content in detoxifying drink variants (mg/100ml of drink)

Minerals	Calcium	Iron	Zinc	Magnesium	Manganese	Selenium (µg/100 ml)	Chromium	Copper
SD	$16.68^{a}\pm0.23$	$0.41^{a}\pm0.004$	$0.248^{a}\pm0.002$	$55.36^{a}\pm0.46$	$0.422^{a}\pm0.005$	$0.441^{a}\pm0.00$	$0.151^{a}\pm0.00$	$0.022^{a}\pm0.00$
LG5	$20.10^{b}\pm0.29$	$0.53^{c}\pm0.009$	$0.261^{b}\pm0.00$	$56.98^{b}\pm0.14$	$0.582^{e}\pm0.005$	$0.474^{b}\pm0.003$	$0.159^{b}\pm0.00$	$0.023^{b}\pm0.00$
LG10	$22.49^{c}\pm0.33$	$0.68^{f}\pm0.005$	$0.277^{d}\pm0.002$	$58.11^{c}\pm0.16$	$0.697^{f}\pm0.004$	$0.508^{c}\pm0.00$	$0.168^{d}\pm0.001$	$0.025^{c}\pm0.00$
LG15	$24.28^{e}\pm0.32$	$0.81^{g}\pm0.006$	$0.292^{e}\pm0.002$	$61.01^{d}\pm0.09$	$0.893^{g}\pm0.010$	$0.545^{e}\pm0.00$	$0.175^{f}\pm0.00$	$0.026^{d}\pm0.00$
CL5	$21.52^{d}\pm0.27$	$0.48^{b}\pm0.002$	$0.262^{c}\pm0.001$	$56.67^{b}\pm0.31$	$0.440^{b}\pm0.003$	$0.517^{d}\pm0.00$	$0.163^{c}\pm0.001$	$0.024^{b}\pm0.00$
CL10	$27.14^{f}\pm0.17$	$0.55^{d}\pm0.005$	$0.299^{f}\pm0.002$	$57.78^{c}\pm0.38$	$0.482^{c}\pm0.004$	$0.593^{f}\pm0.00$	$0.171^{e}\pm0.00$	$0.025^{c}\pm0.00$
CL15	$31.15^{g}\pm0.89$	$0.60^{e}\pm0.004$	$0.329^{g}\pm0.002$	$58.44^{c}\pm0.22$	$0.498^{d}\pm0.003$	$0.853^{g}\pm0.00$	$0.179^{g}\pm0.00$	$0.026^{d}\pm0.001$

All values represent mean±SD; Values in columns followed by different superscripts differ significantly ($p \leq 0.05$)

Tukey-Kramer HSD has been applied for the mineral content of the standard drink and its variants using celery powder and lemongrass powder

Plasma renal function indices: In this study plasma urea, uric acid and creatinine were analyzed to evaluate kidney function. Elevations of kidney biomarkers such as plasma urea, BUN, uric acid and creatinine are considered the reliable and gold standard for investigating drug-induced nephrotoxicity. These parameters are often used to measure renal function because these metabolic waste products are eliminated by kidneys but get retained in renal injury (Wu and Huang, 2018). Table 5 shows the effect of CCl_4 toxicity on renal function biomarkers. Short-term administration of CCL_4 caused a significant ($p \leq 0.05$) increase in urea (114.7%), uric acid (138.6%) and creatinine (144%) as compared to the normal control. These deviated kidney function biomarkers were completely restored ($p \leq 0.05$) near the normal range by feeding lemongrass and celery detoxifying drinks to animals. The data indicate that celery and lemongrass detoxifying drinks ameliorated the deleterious effect of CCl_4 toxicity and maintained renal physiological function and cell integrity. In a healthy kidney, 20% filtered creatinine reaches proximal tubules where it is eliminated but not absorbed. But injured tubules affect normal physiological functioning and thus, increase serum creatinine levels. Urea is synthesized in the liver either from the oxidation of amino acids or from ammonia as a part of the urea cycle. Uric acid is a heterocyclic compound that is a by-product of purine nucleotides. High blood concentrations of uric acid can lead to numerous medical complications like gout and arthritis (Said *et al*., 2019). The data from this study reveals a drastic (144%) increase in creatinine levels in CCl_4 nephrotoxic group as compared to the normal control. Acute Kidney Injury is diagnosed and ensured when serum creatinine level reaches 0.3 mg/dl (26.5 µmol/ L) or is either increased by 1.5 times the baseline in the first 7 days (Khwaja, 2012). CCl_4 also significantly increased the plasma concentration of urea and uric acid as compared to the normal group. A rise in the level of these kidney function biomarkers was also observed in adenine-induced CKD rats thus; indicating nephrotoxicity and renal cell damage (Said *et al*., 2019).

Table 5: Kidney Function Biomarkers of Normal and CCl_4-intoxicated rats

Group	Treatment	Urea (mg/dl)	BUN (mg/dl)	Uric acid (mg/dl)	Creatinine (mg/dl)
I	Normal control	31.94±1.02	14.92±0.48	2.20±0.23	0.75±0.10
II	CCl_4	**68.58^{a}±0.98**	**32.03^{a}±0.46**	**5.25^{a}±0.21**	**1.83^{a}±0.17**
III	Silymarin + CCl_4	40.28^{d}±1.90	18.81^{d}±0.89	2.26^{d}±0.10	0.78^{c}±0.08
IV	SD+ CCl_4	54.14^{b}±3.53	25.28^{b}±1.65	4.28^{b}±0.39	1.24^{b}±0.12
V	LG5+ CCl_4	51.50^{b}±2.20	24.05^{b}±1.03	4.03^{b}±0.16	0.97^{c}±0.26
VI	LG15+ CCl_4	46.40^{c}±1.63	21.67^{c}±0.76	3.41^{c}±0.37	0.89^{c}±0.18
VII	CL5+ CCl_4	45.31^{c}±1.97	21.16^{c}±0.92	3.37^{c}±0.13	0.90^{c}±0.14
VIII	CL15+ CCl4	41.56^{d}±1.85	19.41^{d}±0.86	2.49^{d}±0.16	0.79^{c}±0.13

All values represent mean±SD, n=7 animals; values with the same superscript along the column are not significantly different ($p \leq 0.05$).
Bold values in 2nd row indicate a significant difference ($p \leq 0.05$) between CCl_4 group (Group II) and normal control (Group I)

Tukey-Kramer HSD test has been applied for the given parameters; BUN, blood urea nitrogen

Table 5 shows that lemongrass and celery detoxifying drinks drastically reversed the renal toxicity symptoms and lowered the urea, uric acid and creatinine level in plasma. In rats receiving lemongrass, this can be attributed to the phytochemical constituents of lemongrass that interfere with electrolyte and water reabsorption through renal tubules which consequently enhance the excretion of nitrogenous compounds (Said *et al*., 2019). Besides, celery has a diuretic action that balances electrolytes in plasma by eliminating uric acid (El-Ghany *et al*., 2012). In agreement with the present study, El-Ghany *et al*. (2012) have reported that celery reduced serum urea, creatinine and albumin to globulin ratio and improved total protein and albumin levels as compared to the normal control group and increased food intake and food efficiency ratio in gentamicin induced nephrotoxicity. The preceding data in this study are also in line with the findings reported by Afifah *et al*. (2019). Celery protects against complications of nephrectomy in the rat model and prevents associated anaemia in kidney injury (Afifah *et al*., 2020). The high free radical scavenging capacity of celery has also been reported previously (Danciu *et al*., 2018). In earlier studies, lemongrass has also been reported to reduce BUN, uric acid and creatinine levels in atherogenic rats (Somparn *et al*., 2018) and against cisplatin-induced nephrotoxicity (Haggag, 2015). Lemongrass and celery inhibit lipid peroxidation and increase antioxidant enzyme activity to prevent kidney injury.

Antioxidant status: Malondialdehyde (MDA) is produced from the peroxidation of polyunsaturated fatty acids and is therefore considered to be one of the most reliable biomarkers for cellular oxidative stress (Buege and Aust, 1978). We estimated MDA concentration and antioxidant enzyme activity in erythrocyte lysate to investigate the antioxidant capacity of detoxifying drink variants. Table 6 shows that CCl_4 significantly ($p \leq 0.05$) attenuated the levels of all antioxidant enzymes (SOD, CAT and GPx) and GSH in rats as compared to the normal control group. Also, CCl_4 significantly ($p \leq 0.05$) augmented the level of MDA. Identically, these deleterious changes were similar to the results of previous studies on CCl_4 toxicity (Popovic *et al*., 2006). However, rats treated with celery and lemongrass significantly ($p \leq 0.05$) increased the activity of antioxidants (SOD, CAT and GPx) and also elevated GSH levels as compared to the CCl_4 control group. MDA level in all detoxifying drink variants was significantly ($p \leq 0.05$) reduced. The effect of LG15 and CL15 was as significant as that of silymarin. Moreover, celery drinks exhibited significant progress in renal indices of oxidative stress in comparison with lemongrass. Both celery and lemongrass drastically suppressed oxidative stress and lipid peroxidation as compared to the CCl_4 group. These results are in agreement with the earlier studies (Tanasawet *et al*., 2017; Somparn *et al*., 2018). As per Said *et al*. (2019), lemongrass ameliorated all the kidney function tests in plasma as well as attenuated lipid peroxidation in renal tissues in chronic renal failure induced by adenine. Lemongrass can be safely consumed to 5000 mg/kg without showing any sign of nephrotoxicity and have the potential to protect against renal injury and cell destruction (Ademuyiwa *et al*., 2017).

Table 6: Effect of detoxifying drink on enzymatic parameters in erythrocyte lysate of normal and CCl_4-intoxicated rats

Group	Treatment	SOD (U/mg protein)	GPx (U/mg protein)	CAT (U/mg protein)	MDA nmoles/ ml RBC lysate	% inhibition	GSH (µmole/ml RBC lysate)
I	Normal control	1.74±0.04	10.28±0.12	2.21±0.08	4.78±0.11		4.01±0.14
II	CCl_4	**0.82^{f}±0.09**	**5.83^{e}±0.23**	**1.66^{f}±0.07**	**6.87^{a}±0.14**	0	**3.44^{d}±0.09**
III	Silymarin + CCl_4	1.78^{a}±0.04	9.34^{a}±0.15	2.26^{a}±0.06	4.78^{f}±0.08	30.40	4.01^{a}±0.13
IV	SD+ CCl_4	1.00^{e}±0.12	6.51^{d}±0.27	1.8^{e}±0.05	6.38^{b}±0.05	7.10	3.54^{cd}±0.12
V	LG5+ CCl_4	1.31^{d}±0.06	7.18^{c}±0.17	1.90^{de}±0.05	5.89^{c}±0.13	14.25	3.64^{c}±0.13
VI	LG15+ CCl_4	1.63^{b}±0.04	8.24^{b}±0.16	2.08^{bc}±0.09	5.07^{e}±0.12	26.21	3.84^{ab}±0.06
VII	CL5+ CCl_4	1.44^{c}±0.04	8.01^{b}±0.16	2.00^{cd}±0.07	5.58^{d}±0.09	18.74	3.70^{bc}±0.11
VIII	CL15+ CCl_4	1.79^{a}±0.06	9.09^{a}±0.20	2.18^{ab}±0.07	4.91^{ef}±0.09	28.47	3.98^{a}±0.12

Bold values in 2nd row indicate a significant difference ($p \leq 0.05$) between CCl_4 group (Group II) and normal control (Group I)

Tukey-Kramer HSD test has been applied for the given parameters; SOD, superoxide dismutase; GPx, Glutathione peroxidase; CAT, catalase; MDA, malondialdehyde; GSH, reduced glutathione.

Celery can recover antioxidant enzyme activity and eliminate ROS and NO. Similar to the findings of the present study, celery leaves extract attenuated nephrotoxicity complications induced by gentamicin administration and augmented renal activity of SOD, GPx and CAT activity (Hijazi and Mouminah, 2017). Celery is a rich source of vitamin C and A which are potent antioxidants that minimize free radicals that trigger the inflammatory cascade and repair any tissue damage. Celery also contains minerals and nutrients that aid in the overall physiological function of the kidney and cell integrity (Lonkar *et al*., 2013; Duarah and Gupta, 2018). The protective and healing effect of celery is because of its antioxidant, anti-hypertensive and anti-inflammatory efficacy (Afifah *et al*., 2019). Celery has abundant phenols, phenolic acids, flavonoids, polyphenols and tannins that contribute to its high antioxidant activity (Golubkina *et al*., 2020). Celery can be used as a natural antioxidant in food industries and also in nutritional planning for patients suffering from renal disease (Hijazi and Mouminah, 2017).

The free radical scavenging capacity of celery and lemongrass is elucidated and documented by various studies. Celery successfully alleviated the anxiety-like behavior in the rat by inhibiting ROS impact on tissue injury, lipid peroxidation and enzyme activity (Tanasawet *et al*., 2017). Likewise, lemongrass essential oil (LEO) attenuated the toxic effect of benzo (a) pyrene and protected lung fibroblast from DNA damage (Jiang *et al*., 2016).

Conclusion: It is concluded that lemongrass and celery are effective in ameliorating the deleterious effect of carbon tetrachloride and reversing the symptoms of

kidney diseases by rectifying the kidney function biomarkers. Thus, *Apium graveolens* and *Cymbopogon flexuosus* can be used to formulate plant-based therapeutic drugs to protect the kidney reduce oxidative stress and treat nephrotoxicity. The pharmacokinetics of its constituents and their mechanism of action may authenticate the rationale behind its use in traditional and Ayurvedic medicine. The detoxifying drink variant with 1.5% celery powder was equivalent to silymarin (herbal medicine) in protecting the kidney against CCl_4-induced toxicity. Based on the human equivalent dose (HED) we recommend a daily intake of 200 ml/day of lemongrass and celery detoxifying drink for humans on daily basis for treating nephrotoxicity. The formulated drinks can be further studied in humans to assess its detoxifying effects and other nutritional benefits.

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