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Phytochemical Constituents, Therapeutic Applications and Toxicological Profile of *Cymbopogon citratus* Stapf (DC) Leaf Extract.

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ABSTRACT
The medicinal value of herbs and natural plant products depends on their phytochemical constituents that elicit definite physiological or pathological effects in the human body. *C. citratus* has been extensively consumed globally for its medicinal, cosmetic, and nutritional benefits. Studies on its phytoconstituents have documented the presence of tannins, saponins, flavonoids, phenols, anthraquinones, alkaloids, deoxysugars, and various essential oil constituents in the herb. Secondary active metabolites of a number of components have also been implicated in the varied pharmacological effects of this plant, including its toxicity profile. Contrary to the widely held belief that *C. citratus* is relatively safe for consumption at any dose, recent evidence suggest that factors such as the variation in bioactive constituents and dose/duration of administration could influence its toxicological profile. Although it has a wide range of therapeutic effects, *C. citratus* should be used with caution by individuals with kidney and liver diseases, pregnant or lactating women, patients on antiplatelet medication or clotting disorders, and in combination with drugs that depend on the cytochrome P450 enzyme system for their metabolism. High doses and prolonged usage of *C. citratus* tea or decoctions should be discouraged, and more research on dose consistency is warranted.

Keywords: *Cymbopogon citratus* Stapf, toxicological profile, phytoconstituents, therapeutic applications.

1. Introduction
Herbal medicine and various types of plant-based therapeutic/prophylactic products have been available for centuries and applied in the treatments of diseases throughout history. Worldwide, phytomedicine and herbal medicine are culturally accepted and ubiquitously practiced. Empirical evidence links the phytochemistry of herbs and their toxicological profile. Currently, many herbs consumed by humans have been subjected to research by modern methods in order to substantiate their putative phytochemical and toxicological profiles. The importance of these studies for guiding future herbal medicine cannot be overstated, since most herbs consumed may have some toxic effects, and scientific reports of potential long term toxicity of some commonly consumed herbs are emerging in the literature. The toxicological profile of any herb is dependent on its phytochemistry and the prevailing micro-environmental physical or chemical stressors. The present review focuses on the phytochemistry and toxicological profile of a widely consumed herb *C. citratus*.

C. citratus is an economically important aromatic perennial plant of the Poaceae family that has been used to extract essential oils. It is grown around the world and has a century -long record of extensive therapeutic applications in traditional and Ayurvedic medicine in a number of countries [1, 2]. It is used in herbal medicine for a wide range of applications based on its antibacterial [3], antifungal [4], antiprotozoal [5], anti-carcinogenic [6], anti-inflammatory [7], antioxidant [8], cardioprotective [9], antitussive, antiseptic, and anti-rheumatic activities. It has also been used to inhibit platelet aggregation [10], treat diabetes [11], dyslipidemia, gastrointestinal disturbances [12], anxiety [13] , malaria [14], flu, fever, and pneumonia [15], as well as in aromatherapy. In addition to its therapeutic uses, *C. citratus* is also consumed as a tea, added to non-alcoholic beverages and baked food, and used as a flavoring and preservative in confections and cuisines. In cosmetics, its essential oils are used as fragrance in the manufacture of perfumes, soaps, detergents, and creams [16, 17].

Based on the claims of numerous health benefits derived from this plant, a number of studies were being conducted to investigate its actions, identify its phyto-constituents, and elucidate its toxicological profile in both human and animals, with new chemotypes currently being

developed. Several reviews have already appeared in literature on *C. citratus*, describing its phytochemistry and is uses as a medicinal plant [15, 18]. These reviews provide a general overview of its applications in therapeutics, agriculture, cosmetics, and in food products. However, in light of recently published findings on the phytochemistry and toxicological profile of *C. citratus*, the present review summarizes and updates the findings.

2. Phytochemistry of *C. citratus*

Most of the biological effects ascribed to *C. citratus* extracts have been attributed to its primary bioactive constituents, derived from its leaves, stem, and roots, and their secondary metabolites.

To date, a large number of empirical studies have been carried out aiming to expand our understanding of *C. citratus* phytochemistry - [19], including a number of recently conducted studies. These investigations have shown that the chemical composition of *C. citratus* extracts varies according to the geographical origin, genetic differences, part of the plant used, method of extraction, age/stage of maturity, and season of harvest [20-22]. Despite these differences, a number of classes of compounds are reproducibly found, including tannins, saponins, flavonoids, alkaloid phenols, and anthraquinones. Citral (1), myrcene (2), geranial (3), geraniol (4), limonene (5), burneol (6), citronellol (7), nerol (8), neral (9), α-terpineol (10), elemicin (11), caffeic acid (12), apigenin, luteolin (13), kaempferol, quercetin (14), chlorogenic acid (15), and geranyl acetate (16) are found in the essential oil, along with many compounds yet to be identified [23] (Figures 1 and 2). Additionally, isolation of fumesol, furfurol, isopulegol, isovaleranic aldehyde, L-linanool, methylheptenone, n-decyclic aldehyde, terpineone, p-coumaric acid, valeric esters, and other compounds has been reported [15, 24, 25]. Cheel *et al*. [26] also reported the presence of isoscoparin, swertiajaponin, and orientin in *C. citratus*. A summary of the phytochemicals reported to be present in *C. citratus* is presented in Table 1.

Irrespective of its geographical origin, *C. citratus* contains a high percentage (about 80%) of citral, which is a mixture of terpenoids neral and geranial. This high citral content justifies the large scale commercial cultivation of *C. citratus* in several countries [27], and is responsible for the lemony smell that characterizes the species [15, 28]. A variation in the myrcene constitution (12-15%) in West Indian *C. citratus*, in comparison to the East Indian type has been reported [24, 29]. However, as an exception, the essential oil from the Ethiopian *C. citratus* was found to contain geraniol (40%) as its main compound, followed by citral (13%) and α-oxobisabolene (12%) [30].

A survey by Harborne and Williams [31] presented the occurrence of tricin and flavone C-glycosides in five Cymbopogon species, luteoforol in two species, while sulfated flavonoids and apigiforol were found in only one species. The plant material used for this survey included Australian and Asian Cymbopogon varieties. While both flavones, flavonoids C- and O-glycoside, were reported to be present in the Peruvian variant of *C. citratus* by De Matouschek and Stahl-Biskup [32], the herb variant found in Chile contained only C-glycosyl flavonoids in detectable amounts.

Species differences arise from genetic variations that may directly or indirectly influence the chemical composition. For example, a particular species of *C. citratus* could be rich in a given chemical constituent over the other species because the genetic information it bears encodes for these differences in the formation of that particular chemical. These differences can be exploited using modern biotechnology by genetically engineering certain plant species to produce desirable traits, such as pest resistance, selected chemical constituents, and increased yield at harvest. For example, two *C. citratus* varieties, code named RRL-16 and CKP-25, were developed at the Regional Research laboratory, Jammu, India. These variants contained 0.28 and 0.50% of essential oil, respectively. RRL-16 variant was also reported to contain 79-85% citral, while CKP-25 had 82-85% citral (33). A number of *C. citratus* variants plants are developed by genetic engineering techniques to increase the yield of plants with desirable traits. These include variants called Krishnan Neema, [20], Sugandhi (OD 19), Pragati, Praman, Juma Rosa, OD-408, and Kaveri [24].

Aside from species differences, the method of extraction/preparation of the infusions or decoctions, and the technique used in drying the leaves may also influence the derived bioactive constituents of *C. citratus* and their yield [34, 35]. The extraction methods employed in the processing of *C. citratus* include hydrodistillation, pressurized liquid extraction, gas chromatography/mass spectrometry (GC/MS), microwave-assisted hydrodistillation (MAHD), and the Soxhlet extraction method using water, n-hexane, chloroform, and methanol/ethanol mixture as extraction solvents [21]. Other techniques include steam and water distillation, maceration, empyreumatic distillation, and expression [35].

For example, the phytochemical analyses of *C. citratus* leaves and roots performed by Ewansiha *et al*. [22] detected flavonoids and volatile oil in the hexane extract, while tannins, flavonoids, phenol, carbohydrates, and volatile oil were present in the chloroform extract. In the same study, tannins, flavonoids, and carbohydrates were found in the methanol extract of leaf material, while only tannins and carbohydrates were present in the methanol extract of the roots. Similarly, Schaneberg & Khan [36] reported that a larger relative citral component (86.83%) was obtained by the extraction of the essential oil with hexane, when compared with the extraction using other solvents.

Agro-climatic factors such as soil salinity and water contents could also influence the growth, quality and yield of oil from *C. citratus* [20]. Experiments that took into consideration the environmental conditions in the Philippines observed that a better yield of the oil and higher citral content was obtained from *C. citratus* harvested during the drought season (March to June) [37] , as compared to the rest of the year. Tajidin *et al*. [38] found that early or delayed harvest of *C. citratus* affected the essential oils and citral contents of the plant, with a significantly higher oil content found in plants harvested at 5.5 and 6.5 months growth, as compared to those harvested at 7.5 months. Citral contents appeared to reach peak levels 6.7±0.3 months after planting. In that particular study, a total of 65 compounds were detected in plant material analyzed at all stages of maturity, of which 13 were present at all stages and 7 compounds (β-myrcene, 3-undecyne, neral, geranial, nerol, geranyl acetate, and juniper camphor) had concentrations greater than 1%. Based on these findings, it was recommended that *C. citratus* should be harvested at the appropriate level of maturity to maximize the quality of the essential oils and reduce production costs.

Nutritionally, *C. citratus* contains variable amounts of

electrolytes and minerals (Na+, K+, Ca2+, Cu2+, Mg2+, Mn, Se, P, Fe2+, and Zn2+), vitamins (folate, niacin, pyridoxine, riboflavin, and vitamins A, C, and E), and macronutrients (carbohydrates, proteins, and a small amounts of fat), as reported by Aftab *et al*. [1] . *C. citratus* was also proposed to be a rich nutritional source of Zn2+ [39].

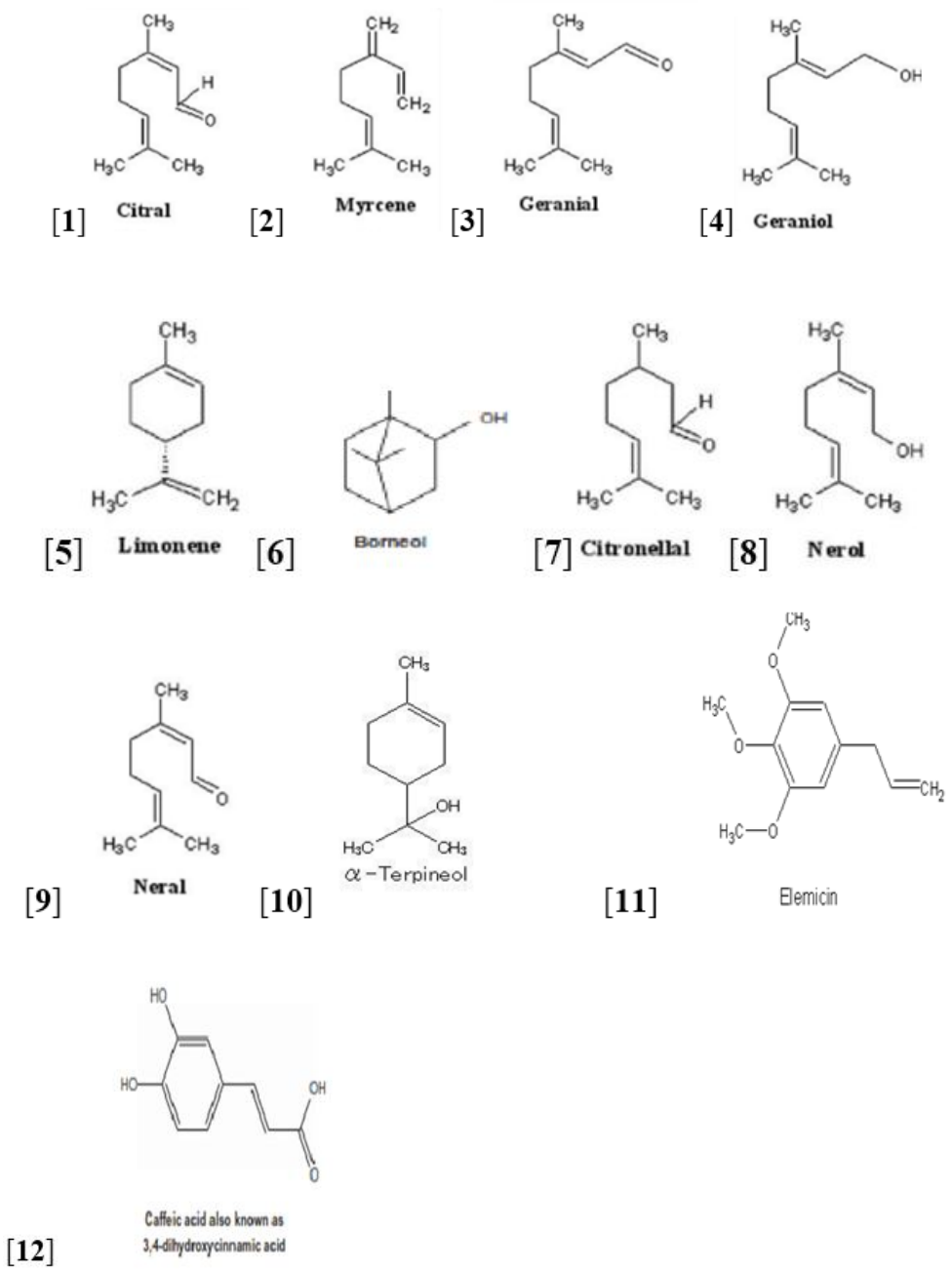

Figure 1

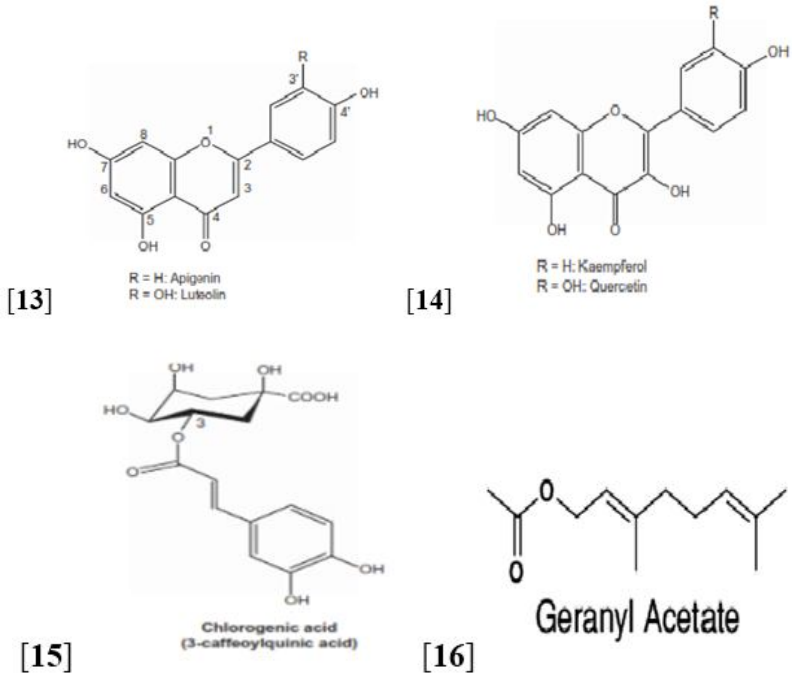

Figure 2

Table 1: Phytochemicals reported in *C. citratus*

Phytonutrients	
Tannins	Saponins
Flavonoids	Alkaloids
Steroids	Essential oils
Phenols	
Mineral contents	
Sodium	Potassium
Calcium	Magnesium
Iron	Zinc
Phosphorus	
Essential oils	
Citral	Burneol
α-terpineol	ß-Myrcene
ß-*O*-Cimene	Allo-*o*-cimene
α-Pinene oxide	Myrcenol
t-Muurolol	Linalool
1-Octyn-3-ol	*trans*-Chrysanthemal
3-Undecyne 3-carvomenthenone	Citronellal
Neral	*trans*-(-)-Carveol
Geranial	Nerol
Citronellol	Methyl-n-nonyl-ketone
Dextro-carvone	Geranic-acid
α-Bergamotene	Isolongifolene-4-5-9-10-dehydro Levo-ß-elemene
γ-Muurolene	α-Gurjunene
α-Muurolene	a-Amorphene ß-Sesquiphellandrene
α-Farnesene	α-Elemol
d-Cadinene	Germacrene-D
Valencene	Viridiflorol
α-Selinene	Humulene
α-Guaiene	*t*-Cadinol
ß-Eudesmol	(*E*,*E*)-Farnesal pimelyl dihydrazide
Di-n-octylphthalate	Geranyl-acetate
***** Phytoconstituents documented hitherto from an extract of *C. citratus* plant leaf [23, 24, 71]	

3. Toxicological profile of *C. citratus*

3.1 Neurotoxicity

Leite *et al*. [40] studied the toxic, hypnotic, and anxiolytic effects of *C. citratus* in fifty healthy volunteers who ingested an infusion of the leaves. In comparing the effects with those in placebo-treated participants under double blind condition, the authors observed no neurotoxic effect.

3.2 Dermatotoxicity

Recent animal studies have shown that citral, a major component of the *C. citratus* oil, can induce skin irritation. Similar skin reactions have been reported in humans. In a study by Motoyoshi *et al.* [41], fifty male volunteers were dermally exposed to 32% citral mixed with acetone for 48 hours. Positive skin reactions, including the presence of erythema, edema, papules, and bullous reaction, were observed. Lemon-scented detergent was also implicated in an outbreak of eczema [42, 43].

3.3 Teratogenicity

Formingoni *et al.* [44] studied the pharmacological effect of *C. citratus* administered daily for 2 months in male and female rats, and in offspring exposed in utero. No effects that could be perceived as signs of toxicity were observed following oral administration of an infusion prepared from the leaves of *C. citratus* to adult rats for 2 months at a dose 20 times larger than the estimated corresponding human dosage. An absence of effects was also noted in both male and female rats, and their offspring when the infusion was administered prior to mating or during pregnancy. In separate animal studies, citral and myrcene were reported to adversely affect the embryos, thereby discouraging the use of *C. citratus* in pregnancy and lactation. A study performed in Brazil by Paumgartten *et al*. [45] found that only very high doses (500 mg/kg) of myrcene increased the pregnancy loss rate and increased the rate of fetal skeletal abnormalities in Wistar rats. Developmental delays, such as delayed eye opening and incisor eruption, were observed in exposed offspring. Another Brazilian study performed by Nogueira *et al.* [46] found an increased rate of skeletal malformations and fetal growth retardation in Wistar rats administered citral at 60 mg/kg dose. An increased pregnancy loss rate also occurred at this dose.

3.4 Nephrotoxicity

The data available in the literature regarding the effects of the *C. citratus* leaf extract on the renal system are conflicting and inconclusive. A study by Hanisa *et al.* [47] found no significant changes in serum biochemical indices of renal function (creatinine, urea, uric acid, protein, and glucose) in rats following administration of the *C. citratus* extract. A separate study by Leite *et al*. [40] made a similar observation in healthy volunteers treated with an infusions prepared from *C. citratus* leaf powder. Similarly, Omer *et al*. [48], conducted a study assessing the effects of *C. citratus* leaf extract supplementation in rabbit feed and found no renal adverse effects, as evidenced by normal serum creatinine and protein levels. Furthermore, two studies suggested that *C. citratus* may have nephroprotective properties [49, 50].

Conversely, Tarkang *et al*. [2] found increased blood urea nitrogen and mild renal tubular distortion in rats following treatment with the *C. citratus* extract for 28 days, suggesting that a high dose or prolonged treatment may be associated with some degree of nephrotoxicity. This finding is supported by a report by Guerra *et al*. [51] of nephrotoxic effects in animals treated with 30 and 80% solutions of *C. citratus* leaf extract.

In another study by Paumgartten *et al*. [45], β-myrcene, an acyclic monoterpene present in the *C. citratus* essential oil, was found to induce kidney enlargement with associated sex-specific hyaline droplet nephropathy. This pathological state was similar to the hyaline nephropathy caused by d-limonene, a monocyclic monoterpene present in the essential oil [52-54]. Past studies have shown that the induction of microsomal enzymes by the bioactive constituents of *C. citratus* is the major pathogenic step in the induction of nephropathy [17, 55]. Interestingly, a growing amount of evidence indicates that the mechanism of d-limonene-induced nephropathy observed in animals may not be clinically relevant, since humans lack the protein that binds to d-limonene [54].

Much like the effects of other loop diuretics, previously documented diuretic and natriuretic effects of *C. citratus* extract [56, 57] could result in an altered glomerular filtration rate (GFR) and, by extension, changes in other indices of renal function with chronic administration. The dose and time-dependent effects, genetic differences, age at harvest, and geographical variations in chemical constituents of the essential oil could also account for the discordant results across published toxicity studies [25, 58]. Regrettably, reliable research data are scant in this regard, and more empirical data on the effect of *C. citratus* on GFR and renal function are needed to either support or counter-indicate its use, particularly in renally compromised individuals such as the elderly, individuals undergoing dialysis, and patients that have undergone a renal transplant. Additionally, further studies are warranted to evaluate the interaction of *C. citratus* extract components with the medications known to adversely affect the kidneys, such as antiretrovirals, aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors [59].

3.5 Hepatotoxicity

A recent study has shown that citral can induce hepatic cytochrome P450 activity, with potential consequences for toxicity and interaction with other drugs [60], especially those that are dependent on this enzyme for metabolism.

In a study by Koh *et al.* [61] aimed at evaluating the hepatoprotective effect of *C. citratus* against carbon tetrachloride (CCl_4)-mediated oxidative damage in rats, the animals were treated with *C. citratus* extract (100, 200, and 300 mg/kg body weight) for 14 days before the administration of a CCl_4 challenge (1.2 mL/kg body weight, p.o.) in the last two days of treatment (13^{th} and 14^{th} day). Hepatic damage was evaluated by assessing standard serum biochemical parameters (alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase), malondialdehyde levels, glutathione (GSH) levels, and altered antioxidant enzymes (catalase, glutathione peroxidase, quinone reductase, glutathione-*S*-transferase, glutathione reductase, and glucose-6-phosphate dehyrogenase). Additionally, CCl_4-mediated hepatic damage was further evaluated by histopathological examination. Most of these changes were alleviated by a prophylactic treatment of animals with *C. citratus* in a dose-dependent manner. The protection was further evident through decreased histopathological alterations in the liver. The results of the

study indicated that the hepatoprotective effect of *C. citratus* can be ascribed to its antioxidant and free radical scavenging property. In a parallel study evaluating the hepatoprotective effects of *C. citratus* against CCL_4-induced damage, El-Serwy [62] found that the addition of *C. citratus* or its oil to the diet improved the nutritional value, in addition to the ratio of liver weight to total body weight. The mean levels of serum cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein (VLDL-C), uric acid, urea nitrogen, creatinine, glucose, aspartate amino transferase (AST), and alanine amino transferase (ALT) were decreased in animals treated with *C. citratus* or its oil, as compared to the positive controls, while high-density lipoprotein (HDL-C) was increased by *C. citratus* treatment. While histopathological examination of the liver in CCl_4-treated group revealed degenerative and necrotic changes, hepatic tissues of animals treated with *C. citratus* or its oil showed a marked reduction in the severity and frequency of these changes. Based on these observations, a high level of *C. citratus* or its oil (5 g/100 g of diet) elicited the strongest beneficial effect on the lipid profile, kidney and liver functions, glucose level, and iron status.

Extract of *C. citratus* protects the integrity of the plasma membrane by reducing the leakage of serum aminotransferase and LDH. At the same time, it also increased the regenerative and reparative capacity of the liver by normalizing the hepatic oxidative stress marker profile. In addition to improving the biochemical profile, reduced CCl_4-induced liver damage was detected on histological examination [61]. On the basis of their results, Koh *et al.* [61] hypothesized that the efficacy of the hepatoprotective effects of the ethanol extract of *C. citratus* may be largely related to the phenolic content and its free radical scavenging activity, which stabilizes the membrane and maintains the normal functioning of hepatocytes.

Phenols such as isoorientin-2-*O*-rhamnoside, chlorogenic acid, and caffeic acid are well-known plant antioxidants and free radical scavengers. These compounds were reported to exhibit hepatoprotective properties [63, 64].

Arhoghro *et al.* [49] investigated hepatoprotective effects of the aqueous leaf extracts of *C. citratus* on cisplatin-induced liver damage. Cisplatin treatment causes an increase in serum ALT levels and a decrease in serum protein concentration, with considerable decreases in body weight, and ratio of liver to body weight. Most of these changes were alleviated by prophylactic treatment with the aqueous extract of *C. citratus* in a dose- and time-dependent manner. The ameliorating effect was further evident through the decreased severity of histopathological alterations in liver tissues samples obtained from animals treated with the aqueous extract of *C. citratus*. In the same study, aqueous leaf extracts of *C. citratus* were found to exhibit anti-hepatotoxic action against cisplatin-induced hepatotoxicity in rats. *C. citratus* extracts, therefore, have the potential for use in the management of liver pathological states, and as a therapeutic adjuvant for the amelioration of cisplatin toxicity.

In a study by Ojo *et al.* [65], antioxidant effects of water extract of green tea and *C. citratus* were investigated in Wistar albino rats. Control and test groups were administered paracetamol (2 g/kg) on the last day of a 10-day treatment with vehicle or a daily dose of 100 mg/kg body weight of green tea and *C. citratus*. The effect of the extracts on serum malondialdehyde levels, catalase activity, and vitamin C were measured, in addition to the evaluation of the effects of the *C. citratus* extract on cholesterol and phospholipids. The extracts of green tea and *C. citratus* elicited a significant antioxidative effect by inhibiting the elevation of serum malondialdehyde levels and catalase activity. Additionally, pre-treatments prevented the depletion of vitamin C. Herbal extracts were able to prevent the alterations in membrane lipids by preventing the paracetamol-induced increase in the cholesterol/phospholipid ratio. On the basis of these results, it was suggested that the extracts of green tea and *C. citratus* could protect against paracetamol-induced lipid peroxidation, possibly by eliminating the deleterious effects of toxic paracetamol metabolites through their antioxidative effects.

However, according to Guerra *et al.* [51], the 30 and 80% fluid plant extracts can elicit hepatotoxic and nephrotoxic effects in animals. These could be perceived as resulting from a high dose and duration of *C. citratus* treatment, suggesting that caution should be exercised when administering high doses over a long period, especially in individuals with indices of compromised hepatic and renal function.

4. Are *C. Citratus* Leaf Extracts Really Toxic?

A number of studies have attempted to answer this question, with conflicting and inconclusive data. Some studies observed toxic effects, while no toxicity was detected by others. However, most of these studies were performed in animals, making the results difficult to apply to humans. Species differences, methods of *C. citratus* processing, duration of intake, site of cultivation and the heavy metal content of the soil, as well as the health status of the individual are only some of the factors that could influence the toxicity of an herbal preparation. Other micro environmental, physical, and chemical stimuli known to elicit toxicity could qualitatively and quantitatively alter the phytochemistry of herbs. Additionally, toxicity of herbal preparations could be due to the adulteration, contamination from toxins during cultivation and extraction, or even from herb interactions with any pharmaceutical agents that the subject may be concurrently taking.

However, *C. citratus* has been used over many years to make caffeine-free tea and as an herbal drink, suggesting that it may be a healthier alternative to caffeine-containing tea products [66]. Akande *et al.* [67] found that, in comparison to other tea brands consumed among Nigerians (Lipton tea, Nescafe, green tea, and Top tea); *C. citratus* tea was a good source of antioxidants such as flavonoids, and therefore a nutritionally acceptable and medicinally valuable beverage. Although some studies have shown that it contains tannins, coumarins, saponins, and anthraquinones, which have been associated with minor toxic effects, the low bioavailability of these phytochemicals in humans may confer a measure of protection against toxicity. The average concentrations of anti-nutrients such as phytate are not significantly higher in *C. citratus*, while cardiac glycosides, cyanates, phlobatannins, and heavy metals like lead and mercury are absent. Therefore, *C. citratus* is considered to be safe for human consumption on the basis of its phytochemical constitution, both nutritional and non-nutritional.

As with other herbs, while *C. citratus* is relatively safe for consumption, caution should be taken in high doses and prolonged intake in both healthy individuals and in diseased states. Additionally, the site of cultivation and methods of extraction can be a concern, as contamination from environmental or industrial sources could render the herb toxic. Empirically, since past research has shown that *C.*

citratus can influence the activities of cytochrome P450 due to its citral contents [68, 69], it could interact with drugs that depend on this enzyme system for their metabolism. However, these interactions need to be confirmed through further studies.

As a general shortcoming in herbal medicine, dosage of administration cannot be as closely regulated as with conventional drugs. However, Salome *et al*. [70] have produced *C. citratus* tablets containing powdered dry *C. citratus* leaves by using acacia and gelatin as binders at concentrations of 2, 4, and 8% w/w. Use of such standardized tablets could help with the monitoring of dose consistency, quality standardization, and control of dosing. However, further studies are still warranted to evaluate the bioavailability of this form, as compared to teas and decoctions,

Though consumed for a wide range of diseases, herbal remedies, including *C. citratus*, should be used with caution in individuals with kidney damage, liver diseases, in pregnant or lactating women, or children under the age of six. High dose and prolonged use of *C. citratus* tea or decoction should be discouraged.

5. Conclusion

C. citratus leaf, stem, and roots are commonly used in herbal medicine. Its essential oils are considered safe for human consumption and are commonly used in aromatherapy. Accumulated evidence has shown that the phytochemicals present in *C. citratus* are responsible for its wide range of pharmacologic and physiologic actions, providing the rationale for its therapeutic applications. However, more empirical studies evaluating the effect of *C. citratus* on humans are needed to substantiate its use in therapeutics. Most of the available studies are animal-based and may not be informative for the assessment of its therapeutic potential in humans. This review provides an overview of the effects of *C. citratus* in health and disease states. There is a need for further research on the potential interaction of *C. citratus* with other drugs, evaluating the effect it may have on their pharmacokinetics and bioavailability, since the herb is most often consumed with other biologically active substances.

6. References

1. Aftab K, Ali MD, Aijaz P, Beena N, Gulzar HJ, Sheikh K *et al*. Determination of Different Trace and Essential Element in Lemon Grass Samples by X-Ray Flouresence Spectroscopy Technique. Int Food Res J 2011; 18:265-270.
2. Tarkang PA, Agbor GA, Tsabang N, Tchokouaha RY, Tchamgoue DA, Kemeta D *et al*. Effect of Long-Term Oral Administration of The Aqueous and Ethanol Leaf Extract of *Cymbopogon citratus* (DC. Ex Ness) Stapf. Ann Biol Res 2012; 3(12):5561-5570.
3. Wannissorn B, Jarikasem S, Siriwangchai T, Thubthimthed S. Anti-Bacterial Properties of Essential Oils From Thai Medicinal Plants. Fitoterapia 2005; 76:233-236.
4. Nakagawa T, Mazzali M, Kang DH, Kanellis J, Watanebe S, Sanchez-Lozada LG *et al*. Hyperuricemia causes glomerular hypertrophy in the rat. Am J Nephrol 2003; 23:2-7.
5. Holetz FB, Ueda-Nakamura T, Filho BD, Cortez DG, Morgado-Diaz JA, Nakamura CV. Effect of Essential Oil of *Ocimum Gratissimum* on the Typanosomatid *Herpetomonas Samuelpessoai*. Acta Protozool, 2003; 42: 269-276.
6. Puatonachokchai R, Kishida H, Denda A, Murata N, Konishi Y, Vinitketkumnuen U. Inhibitory Effects of Lemon Grass (*Cymbopogon citratus* Stapf) Extract on The Early Phase of Hepatocarcinogenesis after Initiation with Ethyinitrosamine in Male Fischer 344 Rats. Cancer Letters, 2002; 183:9-15.
7. Abe S, Maruyama N, Hayama K, Inuoye S, Oshima H, Yamauchi H. Suppression of neutrophils recruitment in mice by geranium essential oil. Mediators Inflamm 2004; 13(1):21-24.
8. Masuda T, Odaka Y, Ogawa N, Nakamoto K, Kuninaga H. Identification of Geranic Acid, a Tyrosinase Inhibitor in Lemongrass (*Cymbopogon citratus*). J Agric Food Chem 2008; 56(2):597-601.
9. Gazola R, Machado D, Ruggiero C, Singi G, Mecado M. *Lippia alba*, *Melissa Officinalis* and *Cymbopogon Citratus* Effects of the Aqueous Extracts on the Isolated Hearts of Rats. Pharmacol Res 2004; 50(5):477-480.
10. Tognolini M, Barocelli E, Ballabeni V, Bruni R, Biandi M, Impicciatore M. Comperative Screening of Plants Essential Oils, Phenylpropanoid as Basic Core for Antiplatelet Activity. Life Science 2006; 78(13):1419-1432.
11. Mansour HA, Newairy AS, Youset MI, Sheweita M.I. Biochemical Study on the Effects of Some Egyptian Herbs in Alloxan-Induced Diabetic Rats. Toxicology, 2002; 170(3):221-228.
12. Carlini EA, De-Contar JP, Siloai-Filho AR, De-Silreiral-Filho NG, Fronchtengarten ML, Bveno OF. Pharmacology of Lemon Grass (*Cymbopogon citratus* Stapf). J Ethnoparmacol 1986; 17(1):37-64.
13. Peigen X. Recent Developments on Medicinal Plants in China. J Ethnopharmacol 1983; 7:95-109.
14. Tchoumbougnang F, Zollo PH, Dagne E, Mekonnen, Y. *In vivo* Anti malaria Activity of Essential Oils from *Cymbopogon Citratus* and *Ocimum Gratissimum* on Mice Injected with Plasmodium Berghei. Planta Medica 2005; 71:20-3.
15. Negrelle RR, Gomes EC. *Cymbopogon citratus* (DC) Stapf: Chemical Composition and Biological Activities. Revista Brasileira De Plantas Medicinais, Botucatu 2007; 9(1):80-92.
16. Lorenzetti BB. Myrcene Mimics the Peripheral Analgesic Activity of Lemongrass Tea. J Ethnopharmacol 1991; 34(1):43-48.
17. De-Oliveira AC, Ribeiro-Pinto LF, Otto SS, Goncalves A. Paumgartten FJ. Induction of liver mono-oxygenase by β-myrcene. Toxicology 1997; 124:135-140.
18. Shah G, Shri R, Panchai V, Sharma N, Singh B, Mann A.S. Scientific basis for the therapeutic use of Cymbopogon *citratus* stapf (lemongrass). J Adv Pharm Technol Res 2011; 2(1):3-8.
19. Chisowa EH, Hall DR, Farman DI. Volatile Constituents of the Essential of *Cymbopogon citratus* Stapf Grown in Zambia. Flavour & Fragrance J 1998; 13(1):29-30.
20. Idrees M, Naeem M, Khan M, Aftab T, Tariq M. Alleviation of salt stress in lemongrass by salicylic acid. Protoplasma 2012; 249(3):709.
21. Nur ABS. Effect of different types of solvent on

extraction of phenolic compounds from *Cosmos caudatus*, 1-16. 2013. Accessed at http://umpir.ump.edu.my/4390/1/CD6378_NUR_AIN_SUKRI.pdf. 5 April, 2014.
22. Ewansiha JU, Garba SA, Mawak JD, Oyewole OA. Antimicrobial Activity of *Cymbopogon citratus* (lemon grass) and its Phytochemical Properties. Frontiers in Science 2012; 2(6):214-220.
23. Bharti SK, Kumar A, Prakash O, Sharma NK, Krishnan S. Essential Oil of *Cymbopogon citratus* against Diabetes: Validation by in vivo Experiments and Computational Studies. Scientific Reports 2013; 2(3):1-9. doi:10.4172/scientificreports.688
24. Akhila A. Essential oil bearing plants: The genus Cymbopogon. Edited by: Anand Akhila. Broca Raton, FL: CRC Press Taylor & Francis Group, 2010.
25. Faruq MO. TLC technique in the component characterization and quality determination of Bangladeshi lemongrass oil. (*Cymbopogon citratus* DC stapf.) Bangladesh J Sci Ind Res 1994; 29:27-38.
26. Cheel J, Theoduloz C, Rodriguez J, Schemeda-Harschmann G. Free Radical and Antioxidants (*Cymbopogan citatus* (DC) Staff). J Agric Food Chem 2005; 53(7):2511-2517.
27. Robbins SJ. Selected markets for the essential oils of lemongrass, citronella and eucalyptus. Tropical Products Institute Report, 1983, 17, 13.
28. Saito ML, Scramin S. Plantas aromáticas e seu uso na agricultura. Jaguariúna: Embrapa, 2000, 45.
29. Koffi K, Komla S, Catherine G, Christine R, Jean-Pierre C, Laurence N. *In vitro* cytotoxic activity of *Cymbopogon citratus* L. and *Cymbopogon nardus* L. essential oils from Togo. Bangladesh J Pharmacol 2009; 4:29-34.
30. Abegaz B, Yohannes PG. Constituents of the essential oil of Ethiopian *Cymbopogon citratus* Stapf. J Nat Prod 1983; 46(3):424-6.
31. Harborne JB, Williams CA. Flavonoid patterns in leaves of the Gramineae. Biochem Syst Ecol 1979; 4:267-280.
32. De-Matouschek BV, Stahl-Biskup E. Phytochemische Untersuchung der nichtflu¨ chtigen Inhaltsstoffe von *Cymbopogon citratus* (DC.) Stapf (Poaceae). Pharm HelV Acta 1991; 66:242-245.
33. Koul VK, Gandotra BM, Koul S, Ghosh S, Tikoo CL, Gupta AK. Steam distillation of lemon grass (*Cymbopogon* spp). Indian J Chem Technol 2004; 11:135-139.
34. Hanaaa AR, Sallamb EYI, El-Leithyc AS, Alya SE. Lemongrass (*Cymbopogon citratus*) essential oil as affected by drying methods. Ann Agric Sci 2012; 57(2):113–116.
35. Nour AH, Ranitha M, Nour AH. Extraction and characterization of essential oils from ginger (*Zingiber Officinale Roscoe*) and Lemongrass (*Cymbopogon citratus*) by microwave assisted hydrodistillation. Int J Chem Environ Engineering 2013; 4(4):221-226.
36. Schaneberg BT, Khan IA. Comparison of extraction methods for marker compounds in the essential oil of lemon grass by cg. J Agric Food Chem 2002; 50(6):1345-9.
37. Oliveros-Belardo L, Aureus E. Essential oil from *Cymbopogon citratus* (D.C.) Stapf growing wild in the Philipines. In: International Congress of Essential Oils, 7, 1977, Manila. Anals. Manila, 1979; 166-8.
38. Tajidin NE, Ahmad SH, Rosennan AB, Azumah H, Munirah M. Chemical composition and citral content in lemongrass (*Cymbopogon citratus*) essential oil at three maturity stages. Afr J Biotechnol 2012; 11(1):2685-2693.
39. Numbiar VS, Matela H. Potential Functions of lemon grass *(Cymbopogon citratus)* in Health and Disease. Int J Pharm Biol Arch 2012; 3(5):1035-1043.
40. Leite JR, Seabra ML, Maluf E, Assolant K, Suchecki D, Tufik S *et al*. Pharmacology of Lemongrass (*Cymbopogon citratus* Stapf) 111. Assessment of Eventual Toxic, Hypnotic and Anxiolytic effects on humans. J Ethnopharmacol 1986; 17(1):75-83.
41. Motoyoshi K, Toyoshima Y, Sato M, Yoshimura M. Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guinea pig, rat, miniature swine and man. Cosmet Toilet 1979; 94:41–48.
42. Rothenberg HW, Menne T, Sjolin KE. Temperature dependent primary irritant dermatitis from lemon perfume. Contact Dermatitis 1977; 3:37–48.
43. Heydorn S, Menne T, Andersen KE, Bruze M, Svedman C, White IR, Basketter DA. Citral, a fragrance allergen and irritant. Contact dermatitis 2003: 49:32–36
44. Formigoni MS, Lodder HM, Filho OG, Ferreira TS, Carlini EA. Pharmacology of lemongrass (*Cymbopogon citratus* Stapf). II. Effects of daily two month administration in male and female rats and in offspring exposed “in utero”. J Ethnopharmacol 1986; 17:65–74.
45. Paumgartten FJ, De-Carvalho RR, Souza CM, Madi K, Chahoud I, Study of the effects of myrcene on rat fertility and general reproductive performance. Braz J Med Biol Res 1997; 31:955-965.
46. Nogueiraa AM, Carvalhoa RR, Souzaa CM, Chahoudb I, Paumgartten FR. Study on the embryofeto-toxicity of citral in the rat. Toxicology 1995; 96(2):105–113.
47. Hanisa H, Hadijah A, Rasedee A, Tarmizi AS. Sub-acute oral administration of *Cymbopogon citratus* stems infusion and its effects on blood biochemical parameters, body and organ weights in rats. J Trop Agric Fd Sc 2011; 39(1):1–7.
48. Omer HA, Elallawy MH, Abdel-Samee LD, Maghraby N. Productive performance of rabbits fed on diets containing lemongrass or active dried yeast. American Eurasian J Agric & Envion Sci 2010; 7(2):179-187.
49. Arhoghro EM, Kpomah DE, Uwakwe AA. Curative potential of aqueous extract of Lemon grass (*Cymbopogon citratus*) on Cisplatin induced hepatotoxicity in albino wistar rats. J Physiol Pharmacol Adv 2012; 2(8):282-294.
50. Ullah N, Khan MA, Khan T, Admad, W. *Cymbopogon citratus* protects against the renal injury induced by toxic doses of aminoglycosides in rabbits. Indian J Pharm Sci 2013; 75:241-6.
51. Guerra MM, Badell JB, Albajés AR, Pérez HB, Valencia RM, Azcuy AL. Toxicologic acute evaluation of the fluid extracts 30 and 80 porciento of *Cymbopogon citratus* (D.C.) Stapf (lemon grass). Rev Cub Plantas Med 2000; 5:97-101.

52. Paiva RO, Madi K, Araujo IB, Souza CM, Kuriyama SN, Faccini A. Beta-mirceno causa nefropatia tubular hialina em ratos machos. Proceedings of XII Reunião Anual daFederação das Sociedades de Biologia Experimental, FESEB, Caxambu, MG, Brazil, 1997, 378.
53. Lehman-McKeeman LD, Rodriguez PA, Takigiku R, Caudill D, Fey ML. D limonene-induced male rat-specific nephrotoxicity: evaluation of the association between d-limonene and alpha 2µ-globulin. Toxicol Appl Pharmacol 1989; 99:250-259.
54. Hard GC, Whysner J. Risk assessment of d-limonene: An example of male rat-specific renal tumorigens. Crit Rev Toxicol 1994; 24:231-254.
55. Freitas JR, Presgrave OF, Fíngola FF, Menezes MC, Paumgartten FR. Effect of ß-myrcene on pentobarbital sleeping time. Brazilian J Med Biol Res 1993; 26:519523.
56. Carbajal D, Casaco A, Arruzazabala L, Gonz AR, Tolon Z. Pharmacological Study of *Cymbopogon citratus* Leaves. J Ethnopharmacol 1988; 25(1):103-7.
57. Caluscusin IR. The effect of twice-a-day intake of lemon grass decoction among hypertensive individuals in Barangay Situbo, municipality of Tampilisan, province of ZamboangadelNorte. ADZU-SOM (http://som.adzu.edu.ph/research/index.php), 2010.
58. Torres R, Ragadio AG. Chemical composition of the essential oil of Philippine *Cymbopogon citratus* (DC) Stapf. Philipp J Sci 1996; 125:147-156.
59. Hernandez-Diaz S, Garcia-Rodriguez LA. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. Am J Med 2001; 110(suppl 3A):20S-7S.
60. Chen M, Long Z, Wang Y, Liu J, Pian H, Wang L *et al*. Protective effect of Saponins on a hypertension target organ in spontaneously hypertensive rats. Exp Therap Med 2013; 5:429-432.
61. Koh PH, Mohd AZ, Igbal M, Igbal M. Antioxidant potential of *Cymbopogon citratus* extract: alleviation of carbon tetrachloride-induced hepatic oxidative stress and toxicity. Hum Exp Toxicol 2012; 31(1):81-91.
62. El-Sewry E. The protective effect of lemongrass and its oil on hepatotoxicity in rats caused by CCL_4. New Egypt J Med 2011; 44(3):58-68.
63. Hoffmann-Bohm K, Lotter H, Seligmann O, Wagner H. Antihepatotoxic C-glycosylflavones from the leaves of *Allophyllus edulis* var. edulis and gracilis. Planta Med 1992; 58:544-548.
64. Orhan DD, Aslan M, Aktay G, Ergun E, Yesilada E, Ergun F. Evaluation of hepatoprotective effect of Gentiana oli Vieri herbs on sub-acute administration and isolation of active principle. Life Sci 2003; 72:2273-2283.
65. Ojo OO, Kabutu M, Bello U, Babayo U. Inhibition of paracetamol induced oxidative stress in rats by extracts of lemon grass (*Cymbopogon citratus*) and green tea (*Camellia sinensis*) in rats. Afr J Biotechnol 2006; 5:1227-32.
66. Blanco MM, Costa CA, Freire AO, Santos JG, Costa M. Neurobehavioural effects of essential oils of *Cymbopogon citratus* in mice. Phytomedicine 2009; 16:265-270.
67. Akande IS, Samuel TA, Agbazue U, Olowolagba BL. Comparative proximate analysis of ethanolic and water extracts of *Cymbopogon citratus* (lemongrass) and four tea brands. Plant Sci Res 2011; 3(4):29-35.
68. Dilberto JJ, Usha G, Birnbaum LS. Disposition of citral in male Fischer rats. Drug Metab Dispos 1988; 16(5):721-7.
69. Dilberto JJ, Srinivas P, Overstreet D, Usha G, Burka LT, Birnbaum LS. Metabolism of citral, an alpha, beta-unsaturated aldehyde, in male F344 rats. Drug Metab Dipos 1990; 18(6):866-75.
70. Salome AC, Emeka CU, Ikechuckwu VO, Sinye AB, Calister EU, Godswill CO. Formulaation and evaluation of *Cymbopogon citratus* dried leaf powder tablets. Afr J Pharmacy and Pharmacology 2012; 6(48):3274-9.
71. USDA. United States Department of Agriculture Research: Agriculture Research Services, Beltville; Gerplasm Resources Information, 2008 (http:www.nal.usda.gov/Fnic/Foodcomp/Search/).