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Technical Literature

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The Safety of Neumentix™ Phenolic Complex K110-42

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KEY CONCLUSIONS

- *Neumentix™ Phenolic Complex K110-42 is a proprietary, water-extracted, natural ingredient made from spearmint. Spearmint has a long history of use as a food, flavoring and medicinal agent.*
- *Based on the in vitro and in vivo studies, Neumentix is safe when taken as recommended at ≤5.4 mg total phenolics as gallic acid equivalents/kg bw/day and/or ≤3.0 mg RA/kg bw/day.*

INTRODUCTION

Spearmint (*Mentha spicata* L.) is one of the more than 7,000 members of the Lamiaceae (also known as Labiatae) family which also include other well-known herbs such as thyme, sage, basil, marjoram, rosemary, hyssop, catnip, lemon balm and lavender (Lamiaceae, 2014). The genus *Mentha* comprises about 25–30 species, including two species of commercially grown spearmint, viz., 'Scotch' spearmint *(Mentha* × *gracilis* Sole) and 'Native' spearmint (*Mentha spicata* L) (Zheljazkov et. al. 2010).

Generally, spearmint is consumed as food and flavoring (Mint Industry Research Council, 2014; Bienvenu et. al., 1999). Historically, spearmint has also been used in folk medicine as an analgesic, antibacterial, antiparasitic, and sedative, and for the management of stress, anxiety and gastrointestinal disorders including nausea, morning sickness during pregnancy and bad breath (Ulbricht, et al. 2010).

SPEARMINT IN THE FOOD SUPPLY AND ITS COMPOSITION

Spearmint is present in the diet mainly as an herb, tea and flavoring ingredient. Spearmint, spearmint extract, and spearmint oil are included in the U.S. Food and Drug Administration (FDA) Generally Recognized as Safe (GRAS) list (21 C.F.R. 182.10 and 182.20). Compositionally, spearmint varies based on its food form and on plant variety, harvest time, and growth location and conditions (Fletcher et al. 2005; Papageorgiou et al. 2008; Chauhan et al., 2009; Hussain et al., 2010; Zheljazkov et. al., 2010a; Zheljazkov et. al., 2010b; Zheljazkov et. al., 2010c). Fresh and dried spearmint leaves are reported to contain carvone, dihydrocarvone, limonene, menthone, β-citronellol, terpineol, cariophillene, linalool, and β-pinene (Antal et al., 2011). Spearmint as a flavoring ingredient typically comprises the essential oil fraction with the primary constituents generally being carvone and limonene, followed by smaller quantities of 1,8-cineole, menthone, menthol, eucalyptol, dihydrocarvone, cis-carvylacetate, myrcene, carveol, and α- and β-pinene (Abd El-Wahab, 2009; Chowdhury et al., 2007; Pelter et al., 2008; Zheljazkov et al., 2010). Water extracts of spearmint, on the other hand, are reported to contain polyphenols including rosmarinic acid (RA) and other caffeic acid derivatives, and eriocitrin, luteolin, luteolin-O-glucoside, apigenin and apigenin-7-O-rutinoside (Dorman et al., 2003; Pereira and Cardoso, 2013).

KEMIN'S PATENTED SPEARMINT PLANTS: KI110 AND KI42

Kemin's proprietary native spearmint (*M. spicata*) lines, KI110 and KI42 were developed by Kemin's Specialty Crop Improvement (SCI) group. These propagated lines were developed from an open-pollinated spearmint

population via conventional selection techniques and are capable of accumulating >100 mg/g rosmarinic acid on a dry weight basis. In contrast, other spearmint varieties generally contain rosmarinic acid in the range of 7.1 to 58.1 mg/g on a dry weight basis (Fletcher et al., 2005a; Fletcher et al., 2005b; Shekarchi et al., 2012).

Kemin's spearmint lines, unlike commercially grown native spearmints which are grown for their essential oil fraction, have significantly higher amounts of naturally occurring rosmarinic acid and no carvone, while commercial spearmints have significant amounts of carvone and minimal levels of rosmarinic acid. Nevertheless, KI110 and KI42 are representative of the significant genetic variation within publically available spearmint varieties already present in the food chain, given the large degree of genetic variation in spearmint lines evaluated from various regions across the globe (Al-Marzouqi et al., 2007; Al-Tawaha et al., 2013; Chauhan et al., 2009; Dhifi et al., 2013; Hussain et al, 2010; Joshi et al., 2013; Orav et al., 2013; Zheljazkov et. al., 2010b; Zheljazkov et. al., 2010c).

COMPOSITION OF NEUMENTIX™ PHENOLIC COMPLEX K110-42

Neumentix is a simple aqueous extract of Kemin's patented spearmint plants KI110 and KI42 and hence, contains the aqueous components of these proprietary plants. Neumentix is comprised of approximately 10.5% protein, 1% fat, 11% dietary fiber, 4% sugars, 22% other carbohydrates, 3.5% moisture and 21% ash and 27% total phenols expressed as gallic acid equivalents (GAE). Further, Ultra High Performance Liquid Chromatography (UHPLC)-Mass Spectrometer (MS) analysis of the phenolic composition of Neumentix also reveals a powerful assortment of phenolic compounds including, but not limited to, rosmarinic acid, salvianolic acids, caffeic acid, caftaric acid, quinic acid and lithospermic acid.

Neumentix also contains minimal levels of monoterpenes. Monoterpenes are compounds that are naturally occurring in spearmint (Council of Europe, 2008) that are suggested to present potential safety issues at high exposure levels (EFSA, 2012). The monoterpenes— camphor, eucalyptol, limonene, carvone, menthofuran, carvacrol and pulegone, were tested for, in Neumentix (unblended extract) and none were found to be present at levels of concern (Table 1).

Table 1. Summary of Monoterpenes (ppm) in various lots of Spearmint Extract (Limit of Quantification (LOQ) <5 ppm)

Monoterpene	LOT# 5-14-2012	LOT# EXSP21213	LOT# 1401110103	LOT# 1402107945	Reference[a]
Camphor	<LOQ	<LOQ	<LOQ	<LOQ	21 C.F.R. 172.510, EAFUS
Eucalyptol[1]	<LOQ	<LOQ	<LOQ	<LOQ	21 C.F.R. 172.510, EAFUS
Limonene	<LOQ	<LOQ	<LOQ	<LOQ	21 C.F.R. 582.60, EAFUS
Carvone	<LOQ	<LOQ	<LOQ	<LOQ	21 C.F.R. 582.60, EAFUS
Menthofuran[2]	<LOQ	<LOQ	<LOQ	<LOQ	EAFUS
Carvacrol[3]	27.2	18.8	16.4	16.7	21 C.F.R. 172.515, EAFUS
Pulegone	<LOQ	<LOQ	<LOQ	<LOQ	21 C.F.R. 172.515, EAFUS

[a]Includes information about the GRAS status (for use in human and/or animal food) of the monoterpene and the listing of the monoterpene in the FDA, Everything Added to Food in the United States (EAFUS), database

[1] Also known as 1,8-cineole.
[2] 4,5,6,7-tetrahydro-3,6-dimethylbenzofuran, CAS 494-90-6
[3] Also known as 2-p-cymenol

THE SAFETY OF NEUMENTIX

The safety of Neumentix was evaluated based on the following ingredient-specific studies: 2 genotoxicity studies, 2 animal studies and 3 human clinical trials. The genotoxicity and animal studies are published in Regulatory Toxicology and Pharmacology (Lasrado et al., 2015). The three Kemin-sponsored clinical trials include an open-label pilot trial (Nieman et. al., 2015), and two randomized double blind placebo controlled trials (Lasrado et al., 2017; Herrlinger et al., 2017). The test article used in all the safety studies including the human study reported below was Neumentix meeting specification (rosmarinic acid between 14.5% - 17.5%).

- **14-Day Repeated Dose Range Finding Toxicity Study**)
  In the 14-day repeated dose range finding toxicity study, oral (gavage) doses of 0 (vehicle control, water), 844.2, 1948.1 and 3896.1 mg Neumentix/kg bw/day (equivalent to 0, 130, 300 and 600 mg of RA/kg bw/day) were administered to male and female Sprague-Dawley rats. The data from the study revealed no consistent, statistically significant, dose-dependent adverse effects in any of the parameters evaluated. The No Observed Adverse Effect Level (NOAEL) was the highest dose tested, 3896.1 mg Neuementix/kg bw/day (equivalent to 1080 mg total phenolics as GAE/kg bw/day or 600 mg rosmarinic acid/kg bw/day).

- **Repeated Dose 90 Days Oral (Gavage) Toxicity Study**
  In the 90-day repeated dose toxicity study (sub-chronic toxicity study), oral (gavage) doses of 0 (vehicle control water), 422.2, 844.2 and 1948.1 mg Neumentix/kg bw/day (equivalent to 0, 65, 130 and 300 mg of RA/kg bw/day) were administered to male and female Sprague-Dawley rats. Although the results of the 14-day dose range finding toxicity study supported a NOAEL of 3896.1 mg Neumentix/kg bw/day (equivalent to 600 mg RA/kg bw/day), a top dose of 1948.1 mg Neumentix (equivalent to 300 mg RA/kg bw/day) was selected. The data from the study revealed no treatment related clinical signs or adverse effects in any of the parameters studied including body weight, food consumption, neurological parameters, hematology, clinical chemistry, gross histopathology and histopathology. However, absolute and relative weights of pituitary and thyroid were significantly increased in mid- and high- dose group animals and absolute and relative weight of the salivary glands were significantly increased in high dose females compared to vehicle control group. Though the variation in the organ weights was statistically significant, there were no corresponding microscopic changes in the respective organs. Hence, a No Observed Adverse Effect Level (NOAEL) for the test item under the testing conditions and doses employed was 1948.1 mg Neumentix/kg bw/day (equivalent to 300 mg/kg bw/day of rosmarinic acid or 540 mg total phenolics as GAE/kg bw/day), the highest dose tested.

- **Ames *Salmonella typhimurium*-Reverse Mutation Assay**
  In the Ames assay, 5 tester strains of *Salmonella typhimurium*, TA98, TA100, TA102, TA1535 and TA1537, were used in the direct plate incorporation method with and without metabolic activation. A preliminary study was conducted to determine doses of Neumentix for the main study (313, 625, 1250, 2500 and 5000 µg/plate). Standard positive controls (benzo-(a)- pyrene, 2-nitrofluorene, sodium azide, 9-aminoacridine, 2 amino anthracene and mitomycin-C) and a negative control (water) were also evaluated. The data from the assay revealed Neumentix to be non-mutagenic at concentrations of 313 to 5000 µg/plate as measured by the Ames bacterial reverse mutation assay in the absence or presence of S9 mix under the conditions of the test employed and when tested in accordance with regulatory guidelines.

- ***In vitro* Cytogenetic Assay Measuring Chromosomal Aberration Frequency**
  In the Chromosomal Aberration test, the blood from healthy male volunteers (human peripheral blood lymphocytes) was used and tested with Neumentix and mitomycin C (positive control) with and without metabolic activation. The data from the test revealed that Neumentix was non-clastogenic at concentrations of 313 to 5000

µg/ml culture both in the absence or presence of S9 mix under the conditions of the test employed and when tested in accordance with regulatory guidelines.

- **Tolerance and Cognitive Function Effects of a Proprietary Spearmint Extract (Neumentix) in Men and Women with Self-Reported Memory Impairment – An Open Label Pilot Study**
  The open-label pilot trial was designed to assess tolerability and the effects on cognition[4] of Neumentix in subjects with self-reported memory impairment. Subjects (N = 11; 8 Females and 3 Males) with a mean age of 58.7 y and body mass index (BMI) of 27.4 kg/m^2 consumed 900 mg of the extract daily for 30 days. Tolerability to the extract was assessed at baseline and at the end of the supplementation period through a gastrointestinal (GI) tolerability questionnaire (Maki et al. 2008), adverse events reported, and clinical laboratory tests including clinical chemistry, whole blood hematology and lipid profiles. The results of the 30-day supplementation with 900 mg Neumentix revealed no significant alteration in GI tolerability, whole blood hematology and no serious adverse events in any of the study subjects. There were however, significant differences in anion gap, calcium, total protein, and heart rate, but these ranges were deemed not to be clinically relevant since the values were within normal biological variability. The results of this study support that supplementation with 900 mg of Neumentix containing 15.4% rosmarinic acid for 30 days is well-tolerated.

- **Effects of a Proprietary Spearmint Extract (Neumentix) on cognitive performance in Men and Women with Age-Related Memory Impairment (AAMI) – Safety Findings**
  The randomized, double-blind, placebo-controlled, parallel study was designed to evaluate the acute and chronic effects of Neumentix on aspects of cognitive function in men and women with AAMI. Healthy men and women 50-70 years of age, with a BMI 18.5-35.0 kg/m^2 who met the criteria for inclusion/exclusion into the study were randomly assigned to one of three treatments: placebo, 600 mg Neumentix (2 x 300 mg capsules/d), or 900 mg Neumentix (2 x 450 mg capsules/d). The treatments were consumed each day with breakfast over a 90-day study period. Compliance with the treatment regimen was assessed at each test visit (baseline, day 45 and day 90) using a study product diary and a count of the remaining study product. Safety was assessed through the evaluation of treatment emergent adverse events (AEs) reported at each of the three study visits, and changes in vital signs, and laboratory values including clinical chemistry profile, whole blood hematology, hormone analysis and lipid profile at baseline and day 90. AEs were assessed at each visit prior to the study product consumption and at the end of each visit and coded according to the World Health Organization (WHO) dictionary with the number of AEs tabulated by body system, preferred (coded) term, severity and relationship to study product for each condition. The results of the 90-day supplementation trial with 600 mg and 900 mg Neumentix revealed no significant differences between the treatment groups and placebo in the occurrence of AEs or in any anthropometric or hemodynamic safety parameters evaluated. The results of this study further confirm that supplementation of healthy adults with 600 mg and 900 mg of Neumentix for 90 days is well-tolerated.

- **Chronic Supplementation of a Proprietary Spearmint Extract (Neumentix) Is Safe and Well-Tolerated in Young Healthy Individuals – Safety Findings**
  The second randomized, double-blind, placebo-controlled, parallel study was designed to evaluate the chronic effects of Neumentix on aspects of cognitive function and safety in recreationally active, men and women. Healthy men and women 18-50 years of age, with a body mass index (BMI) 18.5-35.0 kg/m^2 who met the criteria for inclusion/exclusion into the study were randomly assigned to one of two treatments: placebo or 900 mg Neumentix (2 x 450 mg capsules/d). The treatments were consumed each day with breakfast over a 90-day study period. Compliance with the treatment regimen was assessed at each test visit (day 7, day 30 and day 90) using a study product diary and a count of the remaining study product. Safety was assessed through the evaluation of treatment

[4] Results related to the effects of cognition are not included in this article.

emergent adverse events (AEs) reported at each of the study visits, and changes in vital signs, and laboratory values including clinical chemistry profile, whole blood hematology, inflammatory biomarkers (cortisol, C-reactive protein (CRP) and interleukin-6 (IL-6)), and lipid profile at baseline, day 30 and day 90. AEs were assessed at each visit prior to the study product consumption and at the end of each visit and coded according to the WHO dictionary with the number of AEs tabulated by body system, preferred (coded) term, severity and relationship to study product for each condition. The results of the 90-day supplementation with 900 mg Neumentix revealed no significant differences between the treatment groups and placebo in the occurrence of AEs or in any anthropometric or hemodynamic safety parameters evaluated. The results of this study further confirm that supplementation of healthy adults with 900 mg of Neumentix for 90 days is safe and well-tolerated.

REVIEW OF SPEARMINT SAFETY LITERATURE

There are only a few studies evaluating the safety of spearmint. Akdoğan et al. (2003, 2004a, 2004b, 2004c), Güney et al. (2006) and Kumar et al. (2008) report on studies conducted in male and/or female albino Wistar rats fed spearmint tea ad libitum for 30 consecutive days. These studies suggest that spearmint could be potentially nephrotoxic (Akdoğan et al., 2003), can cause increased lipid peroxidation and hepatic damage in a dose-dependent manner (Akdoğan et al., 2004a), affect hormones such as luteinizing hormone (LH), follicular stimulating hormone (FSH) and testosterone (Akdoğan et al., 2004b; Kumar et al., 2008), cause uterine damage (Güney et al., 2006), depress activities of enzymes including superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase in the hypothalamus (Kumar et al., 2008) and decrease serum iron, unsaturated iron-binding capacity and ferritin (Akdoğan et al., 2004c). However, in all of the above cited studies, the brewing conditions were not standardized with the tea being prepared with 5 grams (“1 heaped teaspoon”) of dried spearmint leaves in 250 ml of boiling water after steeping for 5-10 minutes. Furthermore, the tea (“water”) consumption was not measured, the source of the tea leaves was not identified and the chemical composition of the tea was not analyzed. The dose of spearmint was estimated based on reported standard fluid intake in rats and critical information including food intake, clinical chemistry, and hematology were not reported.

These reported effects were considered when designing and executing the Neumentix safety studies described herein and none of the adverse findings reported were corroborated in the 90-day study with the dry spearmint extract. There were no findings of nephrotoxicity, hepatotoxicity, and uterine toxicity, and the dry spearmint extract was administered as a bolus dose via oral gavage which provides a more accurate dosing than ad libitum administration used in the spearmint tea safety studies cited above.

There is a single publication by Pearson and colleagues (2011) on High Rosmarinic Acid Mint (HRAM) which is a specially bred spearmint which contains about 68 mg RA/g dry weight of leaf tissue and which was used in a randomized double blind controlled pilot study in horses to characterize the effects of HRAM on biomarkers of inflammation in synovial fluid when challenged with intra-articular LPS and to assess safety of HRAM administered through the feed. The horses consumed the feed with HRAM for 24 days at doses of approximately 54 mg/kg bw/day of HRAM, 3.7 RA mg/kg bw/day or 259 mg RA/day. The authors reported positive effects on biomarkers of inflammation such as prostaglandin E2 and glucosaminoglycan, but more importantly, there were no indications of any negative effects on feed and water intake, fecal consistency, general viability, blood chemistry or hematology.

There have been a few publications where spearmint was administered at a significant dose; four, as a tea (Akdogan et al. 2007, Grant et al., 2010, Connelly et al., 2014) and one, as a bolus of solution of spearmint oil (Bulat et al. 1999).

Bulat and colleagues reported significantly increased symptom scores (chest pain, heart burn and regurgitation) in healthy participants after consuming a single bolus of 500 mg spearmint oil dose. However, none of the adverse events were corroborated by measurements of lower esophageal sphincter (LES) pressure or reflux occurrence. Hence, the authors concluded the effects were likely a function of mucosal irritation. Furthermore, even though they attempted to double blind the study, the authors admit that they were unsure about the integrity of the blinding given the pungent odor of spearmint. Additionally, it is difficult to draw any inference from the study by Bulat et al. (1999) that can be applied directly to the recommendations for use of Neumentix since the study was conducted with spearmint oil and Neumentix is an aqueous extract. The spearmint oil also was administered to participants on an empty stomach while Neumentix is meant to be taken with meals. Most importantly, none of the adverse findings related to mucosal irritation were corroborated by the open-label pilot tolerability trial results conducted with Neumentix (Nieman et. al., 2014).

In a study conducted by Akdogan et al. (2007), 21 female patients with hirsutism consumed 250 mL spearmint tea (20 g/L) twice a day for 5 days during the follicular phase of their menstrual cycle. It was found that there was a significant decrease in free testosterone and increase in luteinizing hormone, follicle-stimulating hormone and estradiol, with no significant decreases in total testosterone or dehydroepiandrostenedione sulphate levels after supplementation; meanwhile, there was no change in fasting plasma glucose, aspartate aminotransferase, alanine aminotransferase, total cholesterol, high density lipoprotein, nor low density lipoprotein, although there was a decrease in plasma triglyceride. It should be noted that as there was no placebo or control group in the study, it is not known if the effect on reproductive hormones is caused by spearmint tea consumption; moreover, reproductive hormones in females of childbearing age are expected to vary during a menstrual cycle. Nevertheless, the study did not report any adverse events and the authors concluded that “spearmint can be an alternative to antiandrogenic treatment for mild hirsutism”. Therefore, it can be inferred that there was no safety concern in this study.

Grant et al. (2010) conducted a double-blinded randomized placebo-controlled trial in 42 subjects with polycystic ovary syndrome to investigate the anti-androgen effect of spearmint tea. Subjects were randomized to receive either spearmint tea or a placebo tea, twice a day, for 30 days; they were instructed to drink two cups of tea per day using tea bags with a standardized content of dried tea leaves. The study measured reproductive hormones, the modified Dermatology Quality of Life Index (DQLI) questionnaire and the Ferriman-Galway score as measures for the degree of hirsutism at day 0, 15, and 30. The results suggested that free and total testosterone levels were reduced significantly whereas luteinizing hormone and follicle-stimulating hormone were increased significantly over 30 days in the spearmint tea group but not in the placebo group. The degree of hirsutism scored by the modified DQLI was significantly reduced but not the objective Ferriman-Gallwey ratings of hirsutism in the spearmint tea group. The study specifically stated that “there were no side effect or tolerability issues reported”, suggesting that 30-day spearmint tea consumption is safe in the study population.

In a randomized double-blind trial conducted by Connelly et al. (2014), 62 participants with medically diagnosed knee osteoarthritis received a high RA spearmint tea or a commercially available spearmint tea (control), twice

a day, for 16 weeks. Both teas were supplied in tea bags and participants were instructed to consume two cups of tea per day in a 300 mL mug. The investigators also analyzed chemical contents of the tea and reported both groups consumed 280 mg or 26 mg rosmarinic acid per day in the high rosmarinic acid spearmint tea group, and the control group, respectively. The study recorded adverse events and measured several outcomes related to pain, quality of life, and physical function at baseline and week 16. It was found both groups had significantly improved stiffness and physical disability scores but only the high rosmarinic acid tea group had significantly decreased pain. With regard to adverse events, "no serious adverse events reported during the study", although a few cases of headache (n=2), constipation (n=3), loose bowel movements (n=1), dry mouth (n=1), itchy skin (n=1), and staining of dentures (n=1) were reported from both groups. All of these cases were transient.

SAFE UNDER RECOMMENDED CONDITIONS OF USE

Kemin recommends a dose of 900 mg for Neumentix containing 14.5% RA (approximately 130.5 mg RA) be taken once daily by healthy adult users with meals. For the low RA specification for Neumentix containing 12% RA, 1090 mg of Neumentix (approximately 130.5 mg RA) is recommended. It is also advised that pregnant and nursing mothers consult with their physicians prior to taking this product.

- The NOAEL from the definitive 90-day for Neumentix is
  - 1948 mg/kg bw/day including
  - 540 mg total phenolics as GAE /kg bw/day and/or
  - 300 mg RA/kg bw/day

- The above NOAEL supports the safety of Neumentix for humans (Safety Factor = 100) up to
  - 19.48 mg/kg bw/day including
  - 5.4 mg total phenolics as GAE /kg bw/day and/or
  - 3.0 mg RA/kg bw/day

Accordingly, both high RA Neumentix containing 14.5% RA and low RA Neumentix containing 12% RA are safe when taken as recommended. The estimated daily intake does not exceed the acceptable daily intake (ADI) for the active constituents of the extract viz., 5.4 mg total phenolics as GAE /kg bw/day and/or 3.0 mg RA/kg bw/day. Alternatively, Neumentix is safe at doses of less than 1,363 mg of extract and 378 mg total phenolics as GAE or 210 mg RA for a 70 kg human.

CONCLUSION

Neumentix Phenolic Complex K110-42 is a proprietary, water-extracted, all-natural ingredient that is safe under the recommended conditions of use.

REFERENCES

1. Abd El-Wahab, M. A., 2009. Evaluation of spearmint (*Mentha spicata* L.) productivity grown in different locations under upper Egypt conditions. Research Journal of Agriculture and Biological Sciences. 5, 250-254.
2. Akdoğan, M., Gultekin, F., Yontem M., 2004. Effect of *Mentha piperita* (Labiatae) and *Mentha spicata* (Labiatae) on iron absorption in rats. Toxicol Ind Health. 20(6-10), 119-122.
3. Akdoğan, M., Kilinç, I., Oncu, M., Karaoz, E., Delibas, N., 2003. Investigation of biochemical and histopathological effects of *Mentha piperita* L. and *Mentha spicata* L. on kidney tissue in rats. Hum Exp Toxicol. 22(4), 213-219.

4. Akdoğan, M., Ozguner, M., Aydin, G., Gokalp, O., 2004. Investigation of biochemical and histopathological effects of *Mentha piperita* Labiatae and *Mentha spicata* Labiatae on liver tissue in rats. Hum Exp Toxicol. 23(1), 21-28.
5. Akdoğan, M., Ozguner, M., Kocak, A., Oncu, M., Cicek, E., 2004. Effects of peppermint teas on plasma testosterone, follicle-stimulating hormone, and luteinizing hormone levels and testicular tissue in rats. Urology. 64(2), 394-398.
6. Akdoğan, M., Tamer, M. N., Cüre, E., Cüre, M. C., Köroğlu, B. K., Delibaş, N., 2007. Effect of spearmint (*Mentha spicata* Labiatae) teas on androgen levels in women with hirsutism. Phytother Res. 21(5), 444-447.
7. Al-Marzouqi, A., Rao, M.V., Jobe, B., 2007. Comparative evaluation of SFE and steam distillation methods on yield and composition of essential oil extracted from spearmint (*Mentha spicata* L). J. Liq. Chrom & Rel Tech. 30:463-475
8. Al-Tawaha, A., Al-Karaki, G., Massadeh, A., 2013. Comparative response of essential oil composition, antioxidant activity and phenolic contents in spearmint (*Mentha spicata* L) under protected soilless vs. open conditions. Advances in Env. Biol. 7(5): 902-910
9. Antal, T., Kerekes, B., Sikolya, L., 2011. Influence of drying on the volatile compounds of spearmint (*Mentha spicata* L.). Proceedings of the III European Drying Conference EuroDrying, 2011 http://www.uibcongres.org/imgdb/archivo_dpo11058.pdf (Accessed September 22, 2014).
10. Bienvenu, F., Petersen, L., Edwards, J., 1999. Native and Scotch spearmint oil production in Tasmania and Victoria. RIRDC Publication No 99/147, RIRDC Project No DAV-101A. http://www.ausbushfoods.com/reports/Species/native%20scotch%20spearmint%20-%2099-147.pdf (Accessed: September 22, 2014)
11. Bulat, R., Fachnie, E., Chauhan, U., Chen, Y., Tougas, G., 1999. Lack of effect of spearmint on lower oesophageal sphincter function and acid reflux in healthy volunteers. Aliment Pharmacol Ther. 13(6), 805-812.
12. Chauhan, R.S., Kaul, M.K., Shahi, A.K., Kumar, A., Ram, G., Tawa, A. 2009. Chemical composition of essential oils in *Mentha spicata* L. accession from North West Himalayan region, India. Indus. Crops & Products. 29:654-656
13. Chowdhury, J. U., Nandi, N. C., Uddin, M., Rahman, M., 2007. Chemical constituents of essential oils from two types of spearmint (Mentha spicata L. and M. cardiaca L.) introduced in Bangladesh. Bangladesh Journal of Scientific and Industrial Research. 42, 79-82.
14. Connelly, A.E., Tucker, A.J., Tulk, H., Catapang, M., Chapman, L., Sheikh, N., Yurchenko, S., Fletcher, R., Kott, L.S., Duncan, A.M. and Wright, A.J., 2014. High-rosmarinic acid spearmint tea in the management of knee osteoarthritis symptoms. Journal of medicinal food, 17(12), pp.1361-1367.
15. Council of Europe, 2008. Natural sources of flavorings, Report No. 3
16. Dhifi, W., Jelali, N., Minif, W., Litaiem M., Hamdi N., 2013. Chemical composition of the essential oil of *Mentha spicata* L. from Tunisia and its biological activities. J of Food Biochemistry 37:362–368
17. Dorman, H. J., Kosar, M., Kahlos, K., Holm, Y., Hiltunen, R., 2003. Antioxidant properties and composition of aqueous extracts from Mentha species, hybrids, varieties, and cultivars. J Agric Food Chem. 51, 4563-4569.
18. European Food Safety Authority, 2012. Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements. EFSA Journal 10(5) 2663. Available at www.efsa.europa.eu/efsajournal (Accessed: September 22, 2014).
19. Fletcher, R.S., McAuley C., Kott, L.S. 2005a. Novel *Mentha spicata* clones with enhanced rosmarinic acid and antioxidant activity. Proc. WOCMAP III, Vol. 6: Traditional Medicine and Nutraceuticals Ada Horticulture. 6S0, ISHS. pp31 – 40
20. Fletcher, R. S., Slimmon, T., McAuley, C. Y., Kott, L. S., 2005b. Heat stress reduces the accumulation of rosmarinic acid and the total antioxidant capacity in spearmint (*Mentha spicata* L). Journal of the Science of Food and Agriculture. 85, 2429-2436.
21. Grant, P., 2010. Spearmint herbal tea has significant anti-androgen effects in polycystic ovarian syndrome. a randomized controlled trial. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives, 24(2), pp.186-188.
22. Greaves J. A., Narasimhamoorthy B., Ruden S., Wildgen S., Barkely R. 2012. Spearmint plant (*Mentha spicata* L.) denominated KI-MSEM0110. U.S. Patent application no. US2012/0204283A1
23. Güney, M., Oral, B., Karahanli, N., Mungan, T., Akdoğan, M., 2006. The effect of *Mentha spicata* Labiatae on uterine tissue in rats. Toxicol Ind Health. 22(8), 343-348.
24. Hussain, A., Anwar, F., Shahid, M., 2010. Chemical composition, anitioxidant and antimicrobial activities of essential oil of spearmint (*Mentha spicata* L) from Pakistan. J of Essential Oil Res. 22:78-84

25. Joshi, R. K., 2013. Pulegone and Menthone chemotypes of *Mentha spicata* L. from Western Ghats region of North Western Karnataka. Natl. Acad. Sci. Lett. 36:349-352
26. Kumar, V., Kural, M. R., Pereira, B. M., Roy, P., 2008. Spearmint induced hypothalamic oxidative stress and testicular anti-androgenicity in male rats - altered levels of gene expression, enzymes and hormones. Food Chem Toxicol. 46(12), 3563–3570.
27. Lamiaceae, 2014. Encyclopedia Britannica Online. Retrieved from: http://www.britannica.com/EBchecked/topic/328710/Lamiaceae (Accessed: September 22, 2014).
28. Lasrado, J.A., Trinker, D., Ceddia, M.A. and Herrlinger, K.A., 2015. The safety of a dry spearmint extract in vitro and in vivo. Regulatory Toxicology and Pharmacology, 71(2), pp.213-224.
29. Mint Industry Research Council, 2014. http://www.usmintindustry.org/ (Accessed: September 22, 2014).
30. Papageorgiou, V., Mallouchos, A., Komaitis, M., 2008. Journal of Agricultural and Food Chemistry, 56: 5743-5752.
31. Narasimhamoorthy. B., Greaves, J. A., Ruden, S., Wildgen, S., Barkely, R. 2012. Spearmint plant (*Mentha spicata* L.) denominated KI-MSEM0042. U.S. Patent application no. US2012/0204283A1
32. Nieman, K.M., Sanoshy, K.D., Bresciani, L., Schild, A.L., Kelley, K.M., Lawless, A.L., Ceddia, M.A., Maki, K.C., Del Rio, D. and Herrlinger, K.A., 2015. Tolerance, bioavailability, and potential cognitive health implications of a distinct aqueous spearmint extract. Functional Foods in Health and Disease, 5(5), pp.165-187.
33. Orav, A., Kapp, K., Raal, A. 2013. Chemosystematic markers for essential oils in leaves of Mentha species cultivated or growin naturally in Estonia. Proc. Estonia Academy of Sciences 62,3:175-186
34. Pelter, L. S., Amico, A., Gordon, N., Martin, C., Sandifer, D., Pelter, M. W., 2008. Analysis of peppermint leaf and spearmint leaf extracts by thin-layer chromatography. Journal of Chemical Education. 85, 133.
35. Pereira O. R., Cardoso, S. M., 2013. Overview on *Mentha* and *Thymus* Polyphenols. Current Analytical Chemistry. 9(3), 382-396.
36. Shekarchi, M., Hajimehdipoor, H., Saeidnia, S., Gohari, A. R., Hamedani, M. P. 2012. Comparative study of rosmarinic acid content in some plants of Labiatae family. Pharmacogn Mag. 8(29), 37-41.
37. Ulbricht, C., Costa, D., J, M. G. S., Guilford, J., Isaac, R., Seamon, E., Varghese, M., 2010. An evidence-based systematic review of spearmint by the natural standard research collaboration. J Diet Suppl. 7, 179-215.
38. Zheljakov, V. D., Cantrell, C. L., Astatkie, T., Ebehar, M. W. 2010a. Peppermint productivity and oil composition as a function of nitrogen, growth stages and harvest time. Agron J.102:124-128
39. Zheljazkov, V. D., Cantrell, C.L., Astatkie, T., Hristov, A. 2010c. Yield, content and composition of peppermint and spearmint as a function of harvesting time and drying. J.Agric.Food Chem.58:11400-11407
40. Zheljazkov, V. D., Cantrell, C. L., Astatkie, T., Ebelhar, M. W., 2010. Productivity, oil content, and composition of two spearmint species in Mississippi. Agronomy Journal. 102, 129-133.