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Research Article

Effect of Honey on Altered Thyroid State in Female Wistar Rats

Adewoye E.O*, and Omolekulo T.E

Department of Physiology, College of Medicine, University of Ibadan, Ibadan, Nigeria.

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Abstract

Health promoting and healing potentials of honey have been widely reported. This study was designed to assess the effect of honey on altered thyroid states. Tri-iodothyronine (T_3), Thyroxine (T_4), Thyroid Stimulating Hormone (TSH) levels were estimated. Antioxidant status was determined by measuring the activities of Superoxide Dismutase (SOD) and Malondialdehyde (MDA). Lipid profile was assessed by measuring the serum levels of Cholesterol (CHOL), Triglyceride (TG), Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) in hypothyroid and hyperthyroid female Wistar strain albino rats. The results obtained show that hyperthyroidism caused significant reduction in body weight while treatment with honey completely reversed this effect. In hypothyroid rats, body weight was further increased on treatment with honey. However, there was no significant effect of honey on the levels of T_3, T_4 and TSH in both hypothyroid and hyperthyroid groups compared with control although the hypothyroid animals treated with honey showed significant reduction in the levels of CHOL, TG, LDL, SOD and MDA compared with hypothyroid untreated. Hyperthyroid rats which received honey exhibited significant increases in the levels of CHOL, TG and LDL compared with control. These findings show that although lipid profile and anti-oxidant status were improved in hypothyroid animals treated with honey, the levels of the thyroid hormones were not reversed in the altered thyroid states. This may be attributed to the presence in honey of phenolic compounds which could enhance free radical scavenging activity and reduce lipid peroxidation.

Keywords: Honey, thyroid hormones, lipid profile, anti-oxidant status.

INTRODUCTION

Thyroid dysfunction is a common endocrine disorder in the female homo sapiens and it has been found to lead to either hyperthyroidism or hypothyroidism (Goldman, 1999). Hyperthyroidism is a condition in which the thyroid gland secretes excess thyroid hormones while hypothyroidism is associated with low secretion of these hormones. Hyperthyroidism is common in women while hypothyroidism may occur in all ages affecting different organs and systems of both men and women (Ishikawa *et al.*, 1998, Goldman 1999). The data from the third National Health and Nutrition Examination Survey (NHANES III) showed a 4.6% prevalence of hypothyroidism in the general population, while 9.5% of the Colorado prevalence study participants had elevated levels of thyroid stimulating hormone (TSH) (Canaris *et al.*,2000). Thyroid failure is more common in women and its prevalence rises with age. Hypothyroid patients have increased levels of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) and has been reported to be a common cause of secondary dyslipidemia (Tsimihodimos et al., 1999, Canaris *et al*., 2000). Honey is a natural substance produced by bees and consist basically of a complex mixture of carbohydrates, especially glucose and fructose, organic acids, amino acids, minerals, vitamins, enzymes, pollens, and pigments (Crane 1975, Fallico *et al.*, 2004). The protective potentials of honey as an antioxidant (Frankel et al.,1998), antihyperlipidemic (Molan,1992), anti-inflammatory (Al-Walli, 2003), antibacterial (Gheldof et al.,2003) antidiabetic (Erejuwa et al., 2012), and anticancer agent (Erejuwa, 2014) have been reported. Since honey is commonly consumed as part of normal human diet, the possibility of honey contributing positively to health even in pathological condition cannot be over looked. This study was therefore designed to assess the effect of honey on thyroid hormones (T_3, T_4 and TSH levels), antioxidant status and lipid profile in altered thyroid conditions.

MATERIALS AND METHODS

Animals: Sixty female Wistar strain albino rats (100-120g) were obtained from the Preclinical Animal House, College of Medicine, University of Ibadan, Ibadan, Nigeria. The animals were acclimatized for two weeks, fed with standard commercial rat chow (Pfizer) and water *ad libitum.*

Drugs: Carbimazole (5mg) and Levothyroxine (100ug), produced by Amdipharm Plc, United Kingdom were obtained from Omak Pharmacy Bodija, Ibadan.

Experimental procedure: Altered thyroid states, hypothyroidism and hyperthyroidism were induced with daily oral administration of carbimazole (2mg/100g b.w) and

**Author for correspondence -*
E-mail:elolade@yahoo.com
Tel: +234-8023405879

levothyroxine (5ug/100g b.w) respectively for 35 days (Ayodeji and Roland, 2012) The rats (n=10) were divided into six groups: Group 1 served as control and received 0.5ml of distilled water for 63days, group 2 received honey (1ml /100g b.w) for 63 days, group 3 received carbimazole (2mg/100g b.w) for 35 days followed by honey (1ml/100g b.w) for the following 28 days, group 4 received carbimazole (2mg/100g b.w) for 35 days followed by honey (1ml/100g b.w) for 28 days, group 5 received levothyroxine (5ug/100g b.w) for 35 days followed by distilled water(0.5ml) for 28 days, group 6 received levothyroxine (5ug/100g b.w) for 35 days followed by honey(1ml/100g b.w) for 28 days. Body weights were measured every week during the course of treatment. At the end of the experiment, blood (5mls) was collected through retro orbital sinus into a plain tube and was allowed to clot. The sample was then centrifuged for 15mins at 3000 rev/min to obtain clear serum for further analysis. On the 36th day of treatment,thyroid hormones - T3,T4 and TSH were assayed by standard procedure using ELISA technique to confirm conditions of hypothyroidism and hyperthyroidism and also on days 14 and day 29 of honey administration to assess the effect of honey on the altered thyroid states. After 28 days of honey administration, cholesterol (CHOL), triglyceride (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) were analyzed using Randox Diagnostic kit UK, based on the method of Meiattini *et al*, 1978. Malondialdehyde (MDA) was analyzed using Sigma Aldrich Diagnostic kit, USA based on the method of Yagi, 1998. Superoxide dismutase (SOD) was analyzed using Superoxide Dismutase assay kit from Cayman Chemicals, Michigan, USA based on the method of Malstrom *et al*, 1975.

Statistical Analysis: Data were analyzed using student t test and ANOVA with $P < 0.05$ indicating the level of statistical significance.

RESULTS

Table 1 shows the different weights of the animals during the period of experimentation. As seen from the data, induction of hypothyroid and hyperthyroid states resulted in significant weight gain and weight loss respectively followed by significant increase in weight after honey treatment in the normal, hypothyroid and hyperthyroid groups. The profile of TSH levels in the animals is depicted in Figure 1. Here, treatment of the hypothyroid group with honey did not show any significant effect on the elevated TSH level while the reduced levels of T3 and T4 (Figures 2 and 3) were not altered by administration of honey.

Table 1:
Weights (g) of Rats Before and After Induction of Altered Thyroid State And After Oral Administration of Honey (1ml/100g b.w).

Group	Weight Before Induction	Weight After Induction	Weight After Honey Treatment
Control	115 ± 4.49#	125.6± 6.98#	No Honey
Normal Rats Treated with Honey	120 ± 3.84#	130.6± 4.86#	145.0± 6.62*
Hypo	100.2 ± 1.96	135.0 ± 6.66	149.6± 5.52*
Hyper	118 ± 2.44	99.6 ± 3.12	132.0± 5.83*

HYPO = Hypothyroid rats(Treated with Carbimazole-2mg/100g b.w), HYPER= Hyperthyroid rats (Treated with Levothyroxine - 5ug/100g b.w).#= normal weight of animals (no Induction)
* indicates significant difference in weights. n = 5 *****P < 0.05

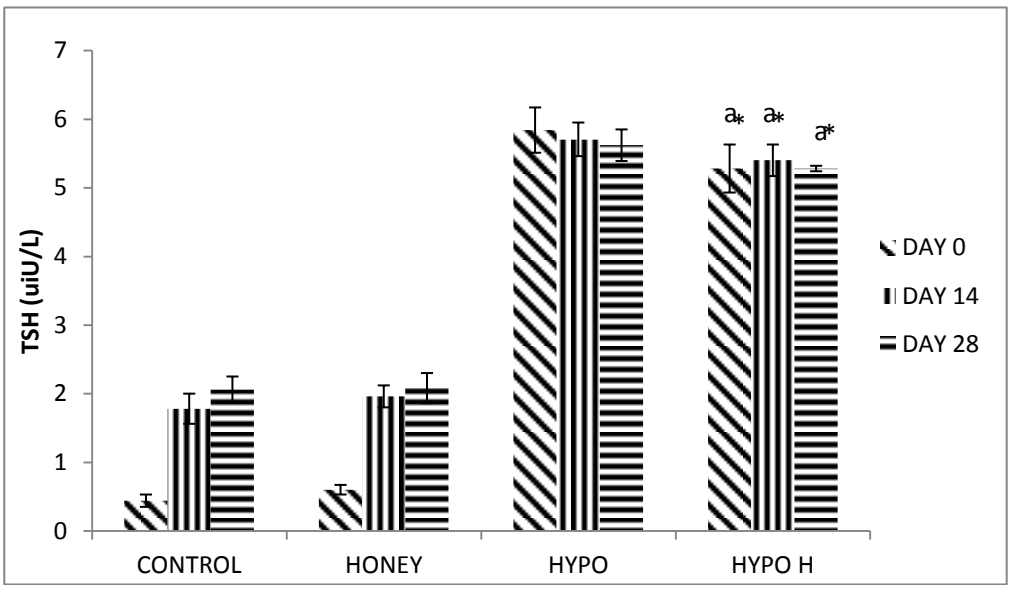

Figure 1:
Effect of Oral Administration of Honey on TSH Level of hypothyroid rats. Carbimazole (2mg/100g b.w) was administered to animals prior to treatment with honey(1ml/100g b.w). TSH levels were assayed on the 14 and 28 days respectively following commencement of administration of honey
HYPO = Hypothyroid rats HYPO H = Hypothyroid rats treated with Honey.* - indicate significant increase compared to control –a- indicate significant increase when compared with normal rats treated with honey. *P < 0.05. n= 5

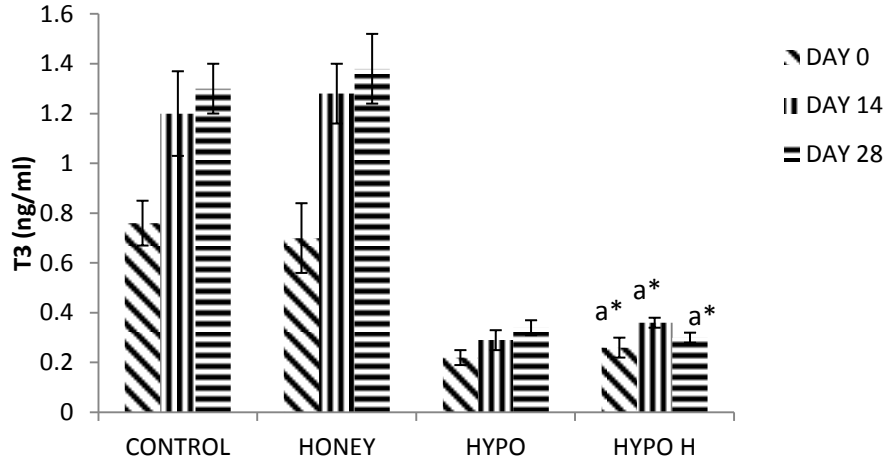

Figure 2:
Effect of oral administration of honey on T_3 level of Hypothyroid rat. Carbimazole (2mg/100g b.w) was administered to animals prior to treatment with honey(1ml/100g b.w). T3 levels were assayed on the 14 and 28 days respectively following commencement of administration of honey HYPO = Hypothyroid rats HYPO H = Hypothyroid rats treated with honey. *indicates significant decrease when compared with control$_a$ indicates significant decrease when compared with normal rats treated with honey. *P < 0.05 n = 5

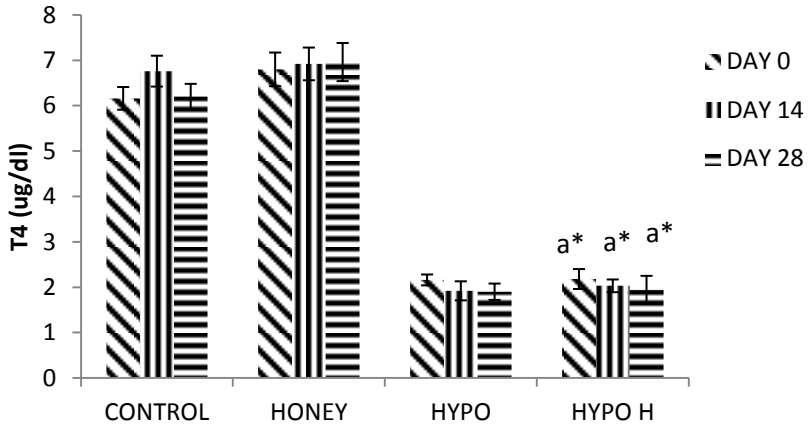

Figure 3: Effect of oral administration honey on T_4 level of hypothyroid rats.
Carbimazole (2mg/100g b.w) was administered to animals prior to treatment with honey(1ml/100g b.w). T4 levels were assayed on the 14 and 28 days respectively following commencement of administration of honey
HYPO = Hypothyroid rats HYPO H= Hypothyroid rats treated with honey(1ml/100g b.w) *means significant decrease when compared with control [a] means significant decrease when compared with normal rats treated with honey. *P<0.05 n = 5

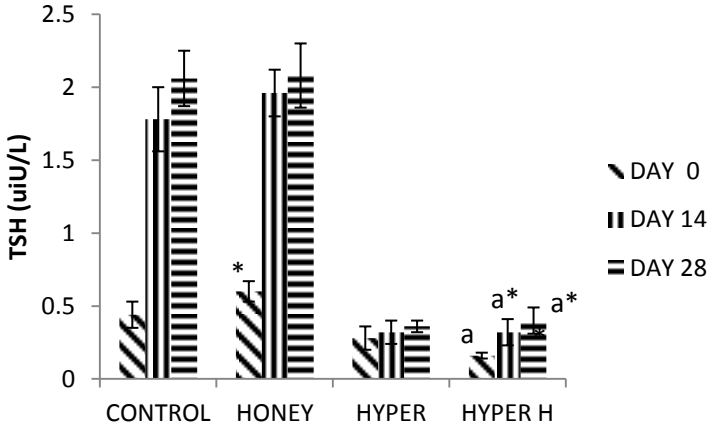

Figure 4:
Effect of oral administration of honey on TSH levels in hyperthyroid rats. Levothyroxine (5ug/100g b.w) was administered to animals prior to treatment with honey(1ml/100g b.w). TSH levels were assayed on the 14 and 28 days respectively following commencement of administration of honey. HYPER = Hyperthyroid rats. HYPER H = Hyperthyroid rats treated with honey(1ml/100g b.w). *means significant difference when compared with control. –a- means significant difference when compared normal rats treated with honey
* P < 0.05 n = 5

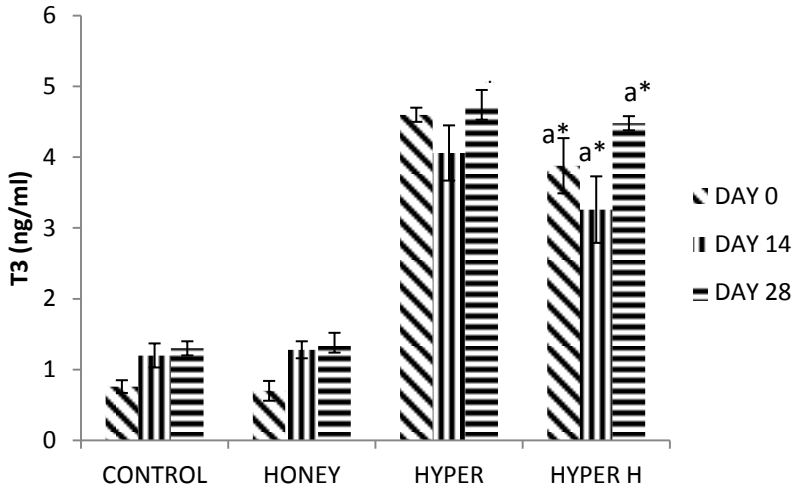

Figure 5:
Effect of oral administration of honey on T_3 levels in hyperthyroid rats. Levothyroxine (5ug/100g b.w) was administered to animals prior to treatment with honey(1ml/100g b.w). T3 levels were assayed on the 14 and 28 days respectively following commencement of administration of honey. HYPER = Hyprthyroid rats HYPER H = Hyperthyroid rats treated with honey(1ml/100g b.w) *means significant increase when compared with control. -a- means significant increase when compared with normal rats treated with honey.* P < 0.05 n = 5

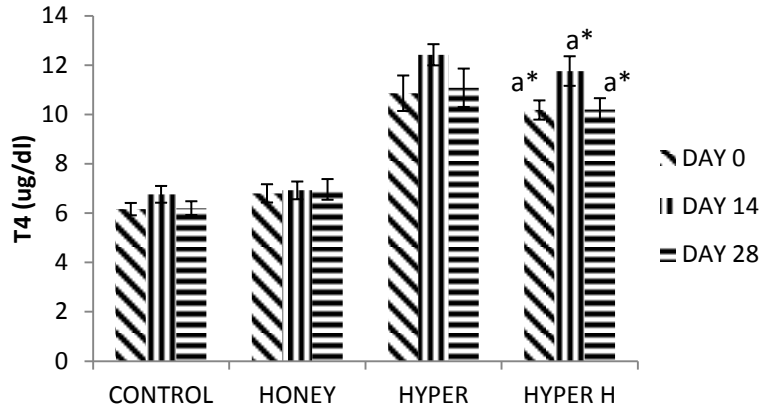

Figure 6: Effect of oral administration of honey on T_4 level in hyperthyroid rats
Levothyroxine (5ug/100g b.w) was administered to animals prior to treatment with honey(1ml/100g b.w). T4 levels were assayed on the 14 and 28 days respectively following commencement of administration of honey. HYPER = Hyperthyroid rats HYPER H =Hyperthyroid rats treated with honey(1ml/100g b.w) * Indicates significant increase compared with control. - a- indicates significant increase compared with normal rats treated with honey. * P < 0.05 n = 5

Table 2:
Effect of oral administration of honey on the lipid profile of hypothyroid rats.

GROUPS	CHOL (mg/ml)	TG (mg/ml)	LDL (mg/ml)	HDL (mg/ml)
Control	42.52 ±5.62	85.07 ±6.56	35.72 ±3.80	21.70 ±2.89
Normal Rats Treated With Honey	46.89 ±4.97	96.35 ±8.74	46.90 ±4.97	19.45±3.05
Hypo	89.08 ±10.61	159.60 ±16.73	80.16 ±3.89	25.19 ±3.78
Hypo H	54.08 ±3.23*	99.51 ±9.49*	47.24 ±4.78*	28.11 ±3.73

HYPO H = Hypothyroid rats treated with honey(1ml/100g b.w). HYPO = Hypothyroid; *indicates significant reduction (P<0.05) when compared with Hypothyroid group.; n = 5 *P < 0.05

Similarly, oral administration of honey to the hyperthyroid group did not show any effect on the reduced TSH level (Figure 4), elevated T3 level (Figure 5) and increased T4 level (Figure 6). Interestingly, administration of honey to the hypothyroid group resulted in increased level of HDL, though not significant (Table 2) but the same treatment reduced significantly ($p<0.05$) the already elevated levels of CHOL, TG and LDL to values that were comparable to those of control animals. On the contrary, honey treatment of the hyperthyroid group resulted in significant ($P<0.05$) elevation of the reduced CHOL and TG levels to values comparable to control. The LDL level was still elevated but HDL levels were within values obtained for control animals (Table 3). Table 4 shows honey treatment of the hypothyroid rats. From these results, it can be seen that SOD levels were significantly ($p<0.05$) reduced compared with control while MDA values were reduced to normal. Table 5 shows honey treatment of the hyperthyroid animals. From these results, SOD levels of the animals increased significantly ($p<0.05$) compared to control while the MDA values reduced to normal.

Table 3:
Effect of oral administration of honey on the lipid profile of hyperthyroid rats

GROUPS	CHOL(mg/ml)	TG (mg/ml)	LDL (mg/ml)	HDL (mg/ml)
Control	45.52±5.62	85.07±6.56	35.72±3.80	21.70±2.89
Normal Rats Treated With Honey	46.89±4.97	96.35±8.74	46.90±4.97	19.45±3.05
Hyper	20.48±2.99	49.69±10.73	51.87±5.08	40.77±5.89
Hyper H	51.56±3.90*	68.30±3.74*	51.35±3.89	26.40±2.86

HYPER H = Hyperthyroid rats treated with honey (1ml/100g b.w). HYPER = Hyperthyroid rats; *indicates significant increase (P<0.05) when compared with hyperthyroid group.; n = 5 *****P < 0.05

Table 4:
Effect of oral administration of honey on oxidative stress markers of hypothyroid rats.

GROUP	SOD (specific activity/min)	MDA (nmol/l)
Control	72.22±2.48	1.00e-6±3.37e-7
Honey	70.34±1.34	1.88e-06±8.56e-7
Hypo	42.45±2.10	2.26e-6±1.39e-7
Hypo H	40.22±2.20*	1.84e-6±6.06e-7

HYPO H = Hypothyroid rats treated with honey(1ml/100g b.w) HYPO = Hypothyroid rats
*inditscates significant reduction (P < 0.05) when compared with control values.n = 5 *****P < 0.05

Table 5:
Effect of oral administration honey on oxidative stress markers of hyperthyroid rats.

GROUP	SOD (Specific activity/min)	MDA (nmol/l)
CONTROL	72.22±2.48	1.00e-6±3.37e-7
HONEY	70.34±1.34	1.88e-6±8.56e-7
HYPER	83.33±1.24	3.20e-6±1.16e-7
HYPER H	80.56±2.08*	1.14e-6±2.46e-7[a]

HYPER H = Hyperthyroid rats treated with honey(1ml/100g b.w). HYPER = Hyperthyroid rats
*indicates significant increase P<0.05 when compared with control
[a] indicates significant reduction P<0.05 when compared with hyperthyroid group
n = 5 *****P < 0.05

DISCUSSION

The data obtained in this study reveal that treatment with carbimazole, an antithyroid agent for 35 days induced hypothyroidism while treatment with levothyroxine induced hyperthyroidism as previously reported by Cooper, (2003). The rise in TSH observed in carbimazole treated group and a decrease in TSH in levothyroxine treated group could be due to the negative feedback mechanism along the hypothalamic-pituitary-thyroid axis as demonstrated by Guyton and Hall, (2010). From this study, oral administration of honey to the hyperthyroid and hypothyroid rats showed no significant difference in the levels of thyroid hormones (T3, T4 and TSH) assayed. The increase in weight observed in the carbimazole treated group is consistent with previous studies that reported increase in weight following induction of hypothyroidism (Thrift et al., 1999). This weight gain has been suggested to be due to decreased metabolic rate as a result of reduced thyroid hormone secretion associated with hypothyroidism and increased glucose storage (Fox et al., 2008). Levothyroxine- induced hyperthyroidism caused significant weight loss in the rats. This has been attributed to an increase in metabolic rate which is synonymous with increased thyroid hormone secretion (Ayodeji et al., 2012). The significant weight gain observed in levothyroxine treated animals following oral administration of honey for 28 days and which was comparable to the body weight in control group could be as a result of long term (28 days) treatment with honey which is a source glucose and this could result to storage as glycogen and fat (Chepulis, 2007, Chepulis et al., 2008). The hypercholesterolemia observed in the hypothyroid group could be due to down regulation of LDL receptors as a result of reduced thyroid hormone secretion hence, the decrease in cholesterol uptake (Shin et al., 2003). However, the mechanism by which honey mediates its anti-hyperlipidemic effect on the hypothyroid group treated with honey is yet to be elucidated.

The observed elevation of oxidative stress status in the hyperthyroid group was most likely induced by the increased thyroid hormone secretion as it occurs in hyperthyroidism and this could be responsible for the increased activity of superoxide dismutase as protective mechanism against elevated oxidative stress status. Hypermetabolism expressed in increased level of thyroid hormones is associated with increased oxygen utilization, increased free radical production and consequently measurable changes in antioxidative factor which is reversed in hypothyroidism (Paller, 1986, Mayer *et al.*, 2004).

Also, an increase in the level of MDA in the levothyroxine group suggested that oxidative damage arising from increased level of reactive oxygen species (ROS) had occurred in cellular structures including membranes and other supramolecules. (Kehrer, 1993). The anti-oxidative effect of honey observed in this study following oral administration of honey to the hyperthyroid group could be due to the presence of antioxidant compounds in honey. Phenolic compounds are present in honey. The compounds are well known to enhance free radical scavenging activity and also reduce lipid peroxidation (Frankel et al., 1998).

In conclusion, the findings from this study show that oral administration of honey reduced previously elevated levels of cholesterol, triglyceride and low density lipoprotein in hypothyroidism unlike in hyperthyroidism and this further confirmed the antihyperlipidemic effect of honey. Honey could therefore be used in the management of hypothyroidism.

REFERENCES

Al-Waili, N. (2003). Intrapulmonary administration of natural honey solution, hyperosmolar dextrose or hypoosmolar distill water to normal individuals and to patients with type-2 diabetes mellitus or hypertension: their effects on blood glucose level, plasma

insulin and C-peptide, blood pressure and peak expiratory flow rate. Eur J Med Res, 8(7):295-303.

Ayodeji FA, Roland EA (2012). The Implication of altered thyroid state on Liver Function. Thyroid Research and Practice 9(3): 84-87

Canaris GJ, Manowitz NR, Mayor G, Ridgway EC (2000). The Colorado thyroid disease prevalence study. Arch Intern Med,160:526–34.

Chepulis L, Starkey N (2008). The long term effects of feeding honey compared with sucrose and a sugar free diet on weight gain, lipid profiles and DEXA measurements in rats. Journal of food science, 73(1): H1-H7.

Chepulis LM (2007). The effect of honey compared to sucrose, mixed sugars, and a sugar-free diet on weight gain in young rats. Journal of food science 72(3):S224-9.

Cooper, DS (2003). Antithyroid drugs in the management of patients with Graves' disease: an evidence-based approach to therapeutic controversies. J Clin Endocrinol Metab, 88:3474-81.

Crane, E. (1975):In Honey: A Comprehensive Survey. Edited by Crane E. William Heinemann, London :439-488.

Erejuwa OO, Sulaiman SA, Wahab MS (2012). Fructose might contribute to the hypoglycemic effect of honey. *Molecules*, 17:1900-1915.

Erejuwa OO, Sulaiman SA, Wahab MS (2014). Effect of honey and its mechanism of action on the development and progression of cancer. Molecules, 19(2): 2497-522

Fallico B, Zappala M, Arena E, Verzera A (2004). Effect of conditioning on HMF content in unifloral honeys. Food Chemistry, 85:305-313.

Fox CS, Pencina MJ, D'Agostino RB, Murabito JM, Seely EW, Pearce EN, Vasan RS (2008). Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample, 168(6):587-92.

Frankel SM, Robbinson GE, Berenbaum MR (1998). Antioxidant capacity and correlated characteristics of 14 unifloral honeys. *J Apicultural Res*, 37:27-31.

Gheldof N, Wang XH and Engeseth NJ (2003). Buckwheat honey increases serum antioxidant capacity in humans. J Agric Food Chem, 51:1500–1505.

Goldman, MB (1999). Thyroid diseases and breast cancer. Epidemiol. Rev, 12:16-28.

Guyton and Hall (2010). A textbook on medical physiology: 11th edition; W.B Saunders xvii: 1322-1326.

Ishikawa, Y.; Genge, B.R.; Wuthier, R.E (1998). Thyroid hormone inhibits growth and stimulates terminal differentiation of epiphyseal growth plate chondrocytes. J. Bone Miner. Res., v.13, p.1398-1411 9.

Kehrer, JP (1993). Free radicals as mediators of tissue injury and disease. Crit. Rev. Toxicol.; 23*:* 21–48.

Malstrom B., Anderson L., Reinhammer B. (1975). The Enzymes XIIIB, Academic Press, New York p.533.

Mayer L., Romic Z., Skreb F., Vrca V.B., Cepelak I., Kirin M (2004). Antioxidants in patients with hyperthyroidism, Clin Chem Lab Med, 42 (2): 154-158.

Meiattini F., Prencipe L., Bardelli F., Giannini G., and Tarli P. (1978). The 4-hydroxybenzoate/4-aminophenazone chromogenic system used in the enzymic determination of serum cholesterol, Am Assoc Clin Chem 24(12):2161-2165.

Molan, PC (1992). The antibacterial activity of honey. Variation in the potency of the antibacterial activity. *Bee World*, 73:59-75.

Paller, MS (1986). Hypothyroidism protects against free radical damage in ischemic acute renal failure. Kidney International, 29:1162-1166.

Shin DJ, Osborne TF (2003). Thyroid hormone regulation and cholesterol metabolism are connected through Sterol Regulatory Element-Binding Protein-2 (SREBP-2) J Biol Chem, 278:34114–8.

Teas J, Bravermann L.E, Kurzer M.S, Pino S, Hurley T.G and Hebert J.R (2007). Seawead and Soy: Companion foods in Asian cuisine and their effects on thyroid function. American Women Journal of medicinal food, 10(1): 90-100.

Thrift TA, Bernal A, Lewis AW, Neuendorff DA, Willard CC, Randel RD (1999). Effect of induced hypothyroidism on weight gains, lactation, and reproductive performance of primiparous Brahman cows, 77(7):1844-50.

Tsimihodimos Vasilis, Mitrogianni Zoi, Moses Elisar (2011). Dyslipidemia associated with chronic kidney disease. Cardiovasc Med J, 5:41-48

Yagi K. (1998). Simple assay for the level of total lipid peroxidases in serum or plasma. Methods Mol. Biol. 108:101-106.