Health, Sports & Rehabilitation Medicine
Vol. 23, no. 4, October-December 2022, 183–188

Quercetin and Curcumin Effects in Experimental Hemithyroidectomy

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Abstract

Background. Thyroid gland is susceptible to oxidative stress. It uses hydrogen peroxide for hormone synthesis and the removal of thyroid tissue may trigger the increase of pro-oxidant processes.

Aims. We investigated the antioxidant effects of quercetin and curcumin on the oxidative stress parameters in rats with hemithyroidectomy.

Methods. Male albino Wistar rats with hemithyroidectomy were used. The animals were randomly allocated in the following groups: group CMC -received carboxymethyl cellulose (CMC) 1%; Que 20 group -quercetin 20 mg/kg/day; Que 40 group -quercetin 40 mg/kg/day; group Euthyrox -1.3 µg/kg/day of sodium levothyroxine; Curcumin 15 group -15 mg/kg/day of curcumin; Curcumin 30 group -revived 30 mg/kg/day of curcumin. The parameters of the oxidative stress were investigated in serum and thyroid homogenate. Thyroxine (T4) and TSH levels were also evaluated.

Results. Quercetin 40 mg/kg/day or Curcumin 30 mg/kg/day administration produced significant modifications: in serum, decreased malondialdehyde (MDA) and increased catalase level; in thyroid gland, decreased MDA, increased glutathione (GSH) and catalase levels. Thyroxine and TSH levels were not modified significantly.

Conclusions. Quercetin and curcumin protected against oxidative stress by decreasing the lipid peroxidation and increasing the antioxidant protection. Curcumin presented the best effects.

Keywords: thyroidectomy, curcumin, quercetin, oxidative stress, antioxidants.

Introduction

Thyroid gland surgical removal is required in several pathological conditions such as: thyroid papillary and follicular carcinomas, medullary thyroid carcinoma, thyroid hyperactivity (thyrotoxicosis), thyroid hypertrophy (goiter), suspicious nodule, non-toxic goiter, toxic multinodular goiter (Biello et al., 2022). Thyroidectomy is performed through different surgical techniques: total thyroidectomy, near total thyroidectomy (both lobes are removed, only a little thyroid tissue is preserved) and hemithyroidectomy (lobectomy) (Cirocchi et al., 2015). Thyroidectomy is a surgical manoeuvre that involves many risks and complications (recurrent laryngeal nerve damage, hemorrhages, infection, postsurgical hypocalcaemia if the parathyroid glands are damaged) (Christou & Mathonnet, 2013). Thyroid tissue removal activates the oxidative stress because of the redox imbalance that may occur in the hormone production: hydrogen peroxide (H_2O_2) is involved in T4 and T3 synthesis (for iodine formation under thyroid-peroxidase action) and its level directs the thyroid gland toward normal or abnormal activity (Mahmood et al., 2021).

Oxidative stress may be significantly reduced by numerous natural extract compounds and among them, curcumin and quercetin proved their efficacy through numerous experiments (Gupta et al., 2013; Trujillo et al., 2013; Yang et al., 2020; Chittasupho et al., 2021).

Quercetin, a flavonoid found in several foods (vegetables, fruit, tea, etc.), may activate the mechanisms involved in the protection against osteoporosis, some cancer types, cardiovascular or respiratory diseases (Boots et al., 2008) through its antioxidant, antitumor, antimicrobial, antifungal, anti-parasite, anti-inflammatory effects (Yang et al., 2020). However, precaution in quercetin administration must be taken in consideration since few studies present its anti-thyroid effects (goiter development and thyroid hormones altered synthesis) (Dos Santos et al., 2011; Giuliani et al., 2014).

Curcumin, a polyphenol from the ginger family used as spicy food additive, in numerous studies showed beneficial effects such as antioxidant, anticancer, anti-inflammatory

Received: 2022, October 30; *Accepted for publication:* 2022, November 3
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https://doi.org/10.26659/pm3.2022.23.4.183

or antibacterial properties (Hewlings & Kalman, 2017), but also protective effects on the thyroid gland and hormone synthesis (Abdelaleem et al., 2018; Dong et al., 2022).

Hypothesis

The experiment started from the hypothesis that quercetin and curcumin may present favorable effects if administered after hemithyroidectomy.

Material and methods

Research protocol

a) Place, period, materials used in the research

The experiment was realized in Physiology Department, Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca, it observed 86/609/EEC Directive and received the approval of the Ethics Committee of the University (no. 245/29.12.2020). Male albino Wistar rats underwent partial thyroidectomy realized with microsurgical instruments sets under aseptic conditions and under anesthesia that was induced by ketamine 10% (2.5 mg/100 gbw) and xylazine hydroxichloride 2% (50 mg/100 gbw). A microscope Foot Pedal IOR 1990 (with magnification 40x) was used during the procedures: peripheral vessels were clamped to avoid the massive bleeding, submandibular glands were identified and separated, the superficial layer of deep cervical fascia and the infrahyoid muscles were dissected, the subjacent tissues were exposed. The right lobe of rats' thyroid was removed.

On the 14th day of the treatment, mild anesthesia induction preceded the collection of blood samples from retro-orbital plexus. Later, the animals were euthanized through profound anesthesia that was realized with ketamine 10% (5 mg/100 gbw) and xylazine hydroxichloride 2% (100 mg/100 gbw) and thyroid samples were collected.

All the administered solutions were purchased from Merck Darmstadt, Germany.

b) Subjects and groups

Forty male albino Wistar rats (weights 180 – 200 g) were randomly allocated into 5 groups (N=8), hosted in cages and maintained in standard environmental conditions (temperature 21 ± 2 °C, relative humidity 55% ±5) with access *ad libitum* to filtered tap water and food, with one week without any procedures prior to the experiment, for their acclimation.

After 72 hours from the surgical procedures, the treatment was introduced. The rats received for 14 days, by oral gavage, at the same time (between 8:00 and 9:00 a.m.), 5 mL/day of solution, as following: *group CMC* - received carboxymethyl cellulose (CMC) 1%; *Que 20 group* - quercetin 20 mg/kg/day; *Que 40 group* - quercetin 40 mg/kg/day; *group Euthyrox* -1.3 µg/kg/day of sodium levothyroxine; *Curcumin 15 group* -15 mg/kg/day of curcumin; *Curcumin 30 group* - received 30 mg/kg/day curcumin.

Applied tests

Oxidative stress investigation

From blood and thyroid homogenate, the oxidative stress parameters were evaluated: malondialdehyde (MDA) (Conti et al., 1991), reduced glutathione (GSH) (Hu, 1994), oxidized glutathione (GSSG) (Vats et al., 2008) and catalase (Pippenger et al., 1998). As an important indicator of the oxidative stress, the GSH/GSSG ratio was calculated and interpreted.

Hormonal determinations

From the blood, the thyroxine level was determined using Rat T4 (Thyroxine) ELISA Kit, and TSH level with Rat TSH ELISA Kit.

c) Statistical processing

For statistical analysis, GraphPad Prism version 5.03 for Windows, GraphPad Software, (San Diego California USA) was used, One-way ANOVA followed by the Post-test Tukey. The significance level was set at $p<0.05$.

Results

All the rats survived the experiment. The investigated parameters presented the following analyzed and interpreted results.

A. Oxidative stress investigation

1. Serum

The lipid peroxidation was investigated in serum through malondialdehyde (MDA), which was decreased significantly by quercetin 40 mg/kg/day compared to CMC ($p<0.01$) and Euthyrox ($p<0.05$) administration, and by curcumin 30 mg/kg/day ($p<0.001$) in comparison with CMC and Euthyrox treatment (Fig. 1A). Glutathione (GSH) levels (Fig. 1B) and ratio GSH/GSSG (Fig. 1D) did not have significant modifications. The group Que 40 presented significant increases of the glutathione disulfide levels only when compared to Que 20 group ($p<0.05$) (Fig. 1C). Serum catalase was increased significantly in Que 40 group compared to CMC ($p<0.01$) and Que 20 ($p<0.05$) groups, and after curcumin treatment: Curcumin 15 group presented significant increases compared to CMC ($p<0.001$) and Que 20 ($p<0.05$) groups while Curcumin 30 group showed significant increases ($p<0.001$) compared to CMC and Que 20 or when compared to Euthyrox group ($p<0.01$) (Fig.1E).

2. Thyroid Gland

In the remaining lobe of thyroid gland, MDA was decreased significantly ($p<0.001$) in Que 40, Euthyrox and Curcumin 30 groups compared to Que 20 group and when compared to CMC group, in Que 40 ($p<0.05$), Euthyrox ($p<0.05$) and in Curcumin 30 ($p<0.001$) groups. The greatest significant reduction ($p<0.001$) of lipid peroxidation was produced by Curcumin 30 mg/kg/day administration compared to CMC, Que 20 and Curcumin 15 groups (Fig. 2A). Glutathione level showed significant increases ($p<0.001$) in all treated groups, compared to control group (CMC). Que 40 increased significantly ($p<0.01$) the GSH level compared to Que 20, Euthyrox and Curcumin 15 groups. In Curcumin 30 group, GSH had the greatest increase ($p<0.001$) compared to CMC, Que 20, Euthyrox and Curcumin 15 groups (Fig. 2B). Glutathione disulfide, compared to CMC group, was decreased significantly in Que 40 ($p<0.05$), Curcumin 15 ($p<0.01$) and in Curcumin 30 ($p<0.05$) groups (Fig. 2C). In remaining thyroid homogenate, compared to CMC group, the ratio GSH/GSSG was significantly increased in Que 20 ($p<0.05$), Que 40 ($p<0.001$), Curcumin 15 ($p<0.01$) and in Curcumin 30 ($p<0.001$). When compared to Euthyrox group, Que 40 and Curcumin 30 showed significant increases ($p<0.01$) of ratio GSH/GSSG (Fig. 2D). Thyroid catalase was increased significantly in Que 40 ($p<0.05$) and in Curcumin 30 ($p<0.001$) groups, compared to CMC group. The administration of curcumin in dose of 30 mg/kg/day increased significantly ($p<0.01$) the catalase level in comparison with Euthyrox treatment (Fig. 2E).

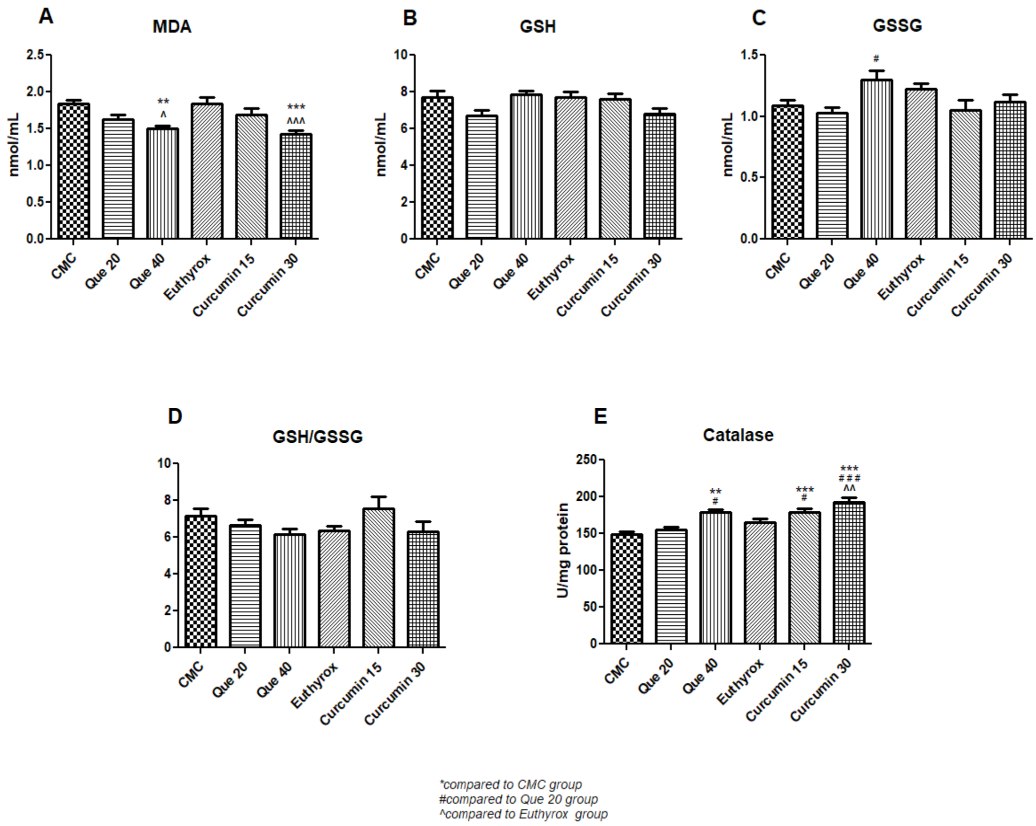

Fig. 1 – The parameters investigated in serum of rats with hemithyroidectomy: MDA, GSH, GSSG, GSH/GSSG, catalase in adult male Wistar rats treated, for 14 days after right thyroid lobe removal, with quercetin, curcumin and Euthyrox compared to carboxymethylcellulose (CMC) administration.

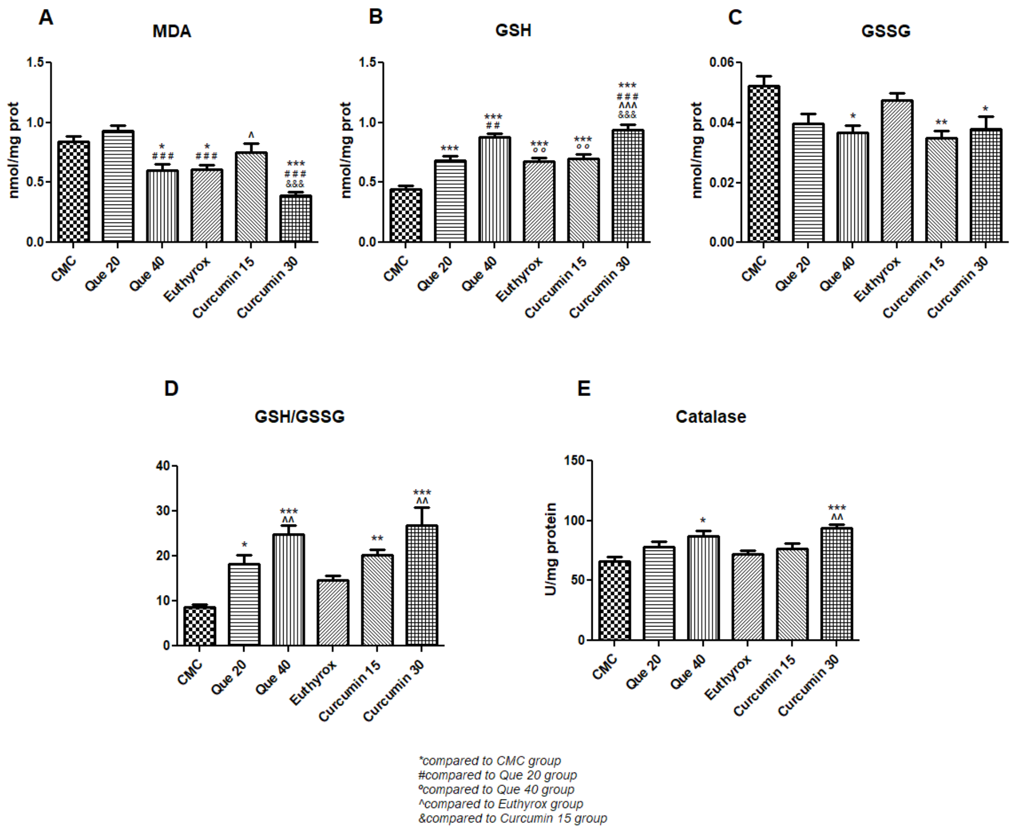

Fig. 2 – Oxidative stress parameters in remaining rats thyroid: MDA, GSH, GSSG, GSH/GSSG, catalase in adult male Wistar rats treated for 14 days after right thyroid lobe removal with quercetin, curcumin and Euthyrox, compared to carboxymethylcellulose (CMC) administration.

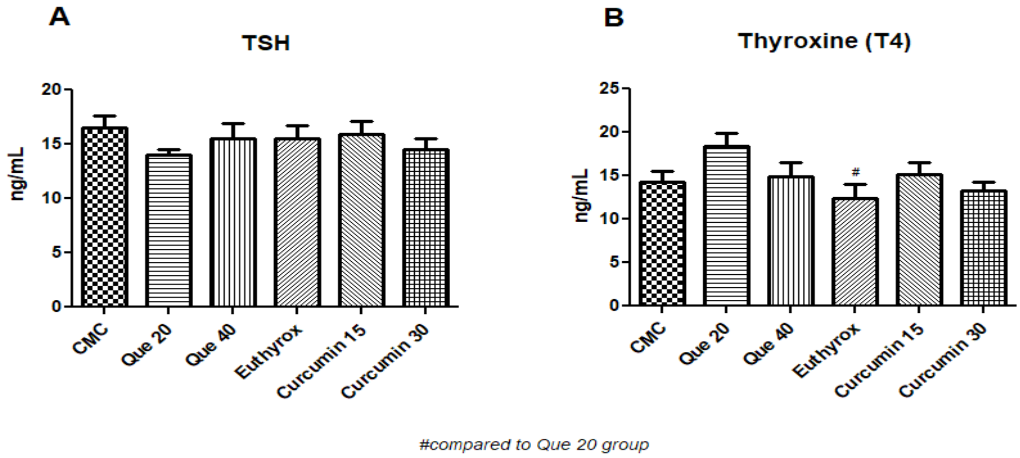

Fig. 3 – TSH and Thyroxine levels in rats with hemithyroidectomy followed by treatment, for 14 days, with quercetin, curcumin and Euthyrox compared to carboxymethylcellulose (CMC) administration.

B. Hormonal Determination

TSH levels did not present significant modifications among the groups of rats with hemithyroidectomy (Fig. 3A). Quercetin administration in dose of 20 mg/kg/day increased significantly ($p<0.05$) the thyroxine (T4) levels compared to Euthyrox treatment (Fig. 3B).

Discussion

Hypothyroidism evolves in parallel with oxidative stress (Chakrabarti et al., 2016), therefore it requires antioxidant protection. In the present study, in rats with experimental hemithyroidectomy, the effects of quercetin and curcumin administrated each in two different doses were evaluated. Many studies present quercetin as a polyphenolic flavonoid with antioxidant effects in diabetes mellitus (Dhanya, 2022), atherosclerosis (Jia et al., 2019), neurodegenerative diseases (Benameur et al., 2021), in exposure to noxious factors (electromagnetic waves, UV light etc) (Xu et al., 2019) and with influences on the thyroid functionality (Capriglione et al., 2021). Curcumin, a natural polyphenol, presents antioxidant properties by inhibiting the hydrogen peroxide, superoxide radical, nitric oxide radical (Joe & Lokesh, 1994), activities that recommend it as a potential effective treatment of the oxidative stress produced by thyroidectomy. In our study we used Euthyrox (sodium levothyroxine) as a positive control, the synthetic T4 hormone used for hypothyroidism treatment.

In serum, malondialdehyde was decreased significantly by quercetin 40 mg/kg/day compared to CMC (vehicle), results that are in concordance with those presented by Lebda et al. in their study performed in rats with propylthiouracil-induced hypothyroidism, treated through gavage with 50 mg/kg/day quercetin (Lebda et al., 2018). Bhattacharya et al. described in their study, performed in adult women with hypothyroidism, the enhancing of lipid peroxidation (Bhattacharya et al., 2014), a pathway that was limited in our study by the administration of quercetin (40 mg/kg/day) but not by Euthyrox (1.3 μg/kg/day) treatment. Curcumin 30 mg/kg/day administration produced lipid peroxidation inhibition, similar result with those presented by Alizadeh and Kheirouri in their review (Alizadeh & Kheirouri, 2019). Significant increased levels of oxidized glutathione were recorded in our study in serum of rats that received 40 mg/kg/day of quercetin, compared to the lower dose (20 mg/kg/day), results that present the pro-oxidant activity of this medication on GSH, in concordance with Mateus et al. study that revealed the quercetin oxidative effects on glutathione (Mateus et al., 2018). As Kohman et al. presented the decreased antioxidant protection as the main cause of the oxidative stress in hypothyroidism (Kochman et al., 2021) the administration of antioxidants may re-establish the redox balance. In our study, quercetin or curcumin oral administration decreased the serum lipid peroxidation and increased antioxidant enzymatic protection (catalase level), the best effects being produced by the curcumin treatment, similar to those presented by Ramírez-Mendoza et al. in their study performed in rats exposed to ozone and treated with this natural polyphenol from turmeric (Ramírez-Mendoza et al., 2022). The significant serum catalase increases in the rats that received 40 mg/kg/day of quercetin is in concordance with the results presented by Demkovych et al. in their experiment performed in rats with experimental periodontitis treated for 7 days with this natural compound, 100 mg/kg intramuscular injection (Demkovych et al., 2019).

In the remaining thyroid tissue, quercetin 40 mg/kg/day, Euthyrox or curcumin administration decreased significantly the lipid peroxidation, a process that is related to hypothyroidism (Chakrabarti et al., 2016). The greatest decrease of MDA in the thyroid tissue was produced by curcumin 30 mg/kg/day administration, result that is concordant with those presented by Abd El-Twab and Abdul-Hamid in their study performed in rats with lithium-induced thyroid impairment but treated with 60 mg/kg/day of curcumin in oral administration, for 6 weeks (Abd El-Twab & Abdul-Hamid, 2016). The antioxidant protection in thyroid tissue was stimulated by both natural polyphenols, the best effects being realized by the curcumin administration in dose of 30 mg/kg/day. Our results are in concordance with those provided by Kumar and Mahobiya in their study on thyroid of mice exposed to *E. Coli,* treated with mitochondria-targeted curcumin (Kumar & Mahobiya 2017). Quercetin 40 mg/kg/day produced a significant increase of catalase level in the remaining thyroid tissue of rats, result that is concordant to that presented by Sriraksa et al. in their experiment performed in rats with experimental Parkinson's disease, when administration of quercetin stimulated the increased of catalase in high levels in hippocampus (Sriraksa et al., 2012). The greatest increase of catalase level was realized by curcumin administration in dose of 30 mg/kg/day, result that is in concordance with those presented by Abd El-Twab and Abdul-Hamid, but at a higher dose (60 mg/kg/day) (Abd El-Twab & Abdul-Hamid, 2016).

Several authors reported the inhibitory effect of higher doses of quercetin (50 mg/kg/day) after intraperitoneal administration (Giuliani et al., 2014), results that we did not record, perhaps because of the administration route that realized a different bio-distribution of the investigated polyphenol metabolites (Dos Santos et al., 2011).

In the present study, TSH and thyroxine levels were evaluated but the results did not present important modifications. Increases of TSH were reported by Ozaki et al. (Ozaki et al., 2012) in their research performed in mice with partial thyroidectomy, effects that we did not record. The same researchers presented decreases of T4 levels, results that we observed, too. The non-significant modifications of TSH recorded in our study in the treated groups may be explained by the unaffected type 2-5'/3' deiodinase in the pituitary gland and CNS, even in severe stressful conditions (Gereben & Salvatore, 2005), the administered treatment efficiently preserving the function of hypothalamus-pituitary-thyroid (HPT) axis.

Conclusions

1. In serum, curcumin 30 mg/kg/day administration presented the best effects on oxidative stress, with significant decreases of lipid peroxidation and significant increases of the catalase level.

2. In the thyroid gland, curcumin 30 mg/kg/day administration had the best effects on oxidative stress, decreasing significantly the MDA and increasing significantly the antioxidant protection (GSH/GSSG ratio and catalase level).

3. Euthyrox administration decreased significantly the lipid peroxidation only in the thyroid tissue.

Acknowledgement
We thank Nicoleta Decea, Principal Chemist from the Oxidative Stress Laboratory, Department of Physiology, Iuliu Hatieganu University of Medicine and Pharmacy for the support.

Conflict of interests
None declared.

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