Grape seed proanthocyanidin extract or spirulina platensis alleviates blood biochemical and hepatic molecular derangements of experimentally-induced thyroid dysfunction in rats

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ABSTRACT

Hyper- or Hypothyroidism is an overactive or underactive thyroid gland that prevents the body from operating properly. The potential therapeutic effects of spirulina platensis and GSPE on experimental hyperthyroidism and hypothyroidism in rats were evaluated. A total 96 rats were divided into two main experimental groups: Experiment A: carbimazole-induced hypothyroidism (1.8 mg/kg b. wt.) and experiment B: induced hyperthyroidism (50, 100, 200 µg/kg b. wt.) for the first three weeks, respectively. The administered GSPE dose (150 mg/kg b. wt./day) and Spirulina (300 mg/kg b. wt./day) for 3 weeks. The hyperthyroidism experiment (A) six sets of rats were used: Group 1 (control normal), Group 2 (hyperthyroidism), Group 3 (GSPE Protected): GSPE administered for the first 3 weeks and continued with thyroxine for another 3 weeks. Group 4 (GSPE treated): thyroxine administered for 3 weeks, followed by GPSE as in group 3. Group 5 (Spirulina Protected); spirulina and thyroxine administration as in group 3. Group 6 (Spirulina treated): spirulina and thyroxine administration in group IV. The hypothyroidism experiment (B) rats divided also into 6 groups like to the above design in hyperthyroidism experiment (A) but carbimazole dose was stable (1.8 mg/kg b. wt.) in the 3 weeks. In hyperthyroidism spirulina and GPSE significantly increased serum total cholesterol, triacylglycerols with down regulation of liver Caspase-8 and significant upregulation of Bc12 gene. In hypothyroidism spirulina and GPSE exhibited down regulation in liver miRNA 224, PKCα with significant upregulation of miRNA 382 gene in hyperthyroid rats. Spirulina and grape seed may treat and prevent hyperthyroidism or hypothyroidism in rats.

1. INTRODUCTION

The thyroid gland is the site for the synthesis of the thyroid hormones. The amino acid tyrosine is the source of two hormones that contain iodine. In the liver, thyroid hormones regulate cholesterol homeostasis, production of bile acids and the metabolism of fatty acids (Mullur et al., 2014). In contrast to hypothyroidism, which is characterized by elevated cholesterol levels, decreased lipolysis, and increased gluconeogenesis, hyperthyroidism generates a hyper-metabolic state that is marked by decreased cholesterol levels, increased lipolysis, and increased gluconeogenesis (Cicatello et al., 2018). L-thyroxine and carbimazole, two medications used to treat thyroid conditions, are also utilized in animal experiments to experimentally cause hypothyroidism and hyperthyroidism (Treesh and Khair, 2014). Drugs that include L-thyroxine affect oxidative stress and have an impact on lipid profiles (TC, TG, HDL, LDL, VLDL). Hyperthyroidism is a hyper-metabolism resulting from increased freeT4 and/or free T3 serum levels (Işman et al., 2003). This hypermetabolic state is associated with an increase in the prooxidant to antioxidant ratio, which leads to oxidative stress (Kim 2012; Hashem 2016). People with hyperthyroidism might end up with common health problems such as cardiovascular diseases (heart failure and increased risk of heart attack), diabetes mellitus, oxidative damage to the liver and osteoporosis (Kim et al., 2012). On the other hand, deficiency, or absence of Thyroid hormone (TH) causes hypothyroidism. One of the most prevalent thyroid conditions in people, either congenital or acquired, is this one (Ayuob, 2016). All bodily processes slowdown in the hypothyroid state, which is a complex hormonal dysfunction (Hayat et al., 2010). In hypothyroidism, the basal metabolic rate is decreased, and the production of reactive oxygen species (ROS) is increased (Rabeh and El-Ghandour, 2016). Metabolic depression resulting from hypothyroidism has been associated with a decrease in oxidant production (Işman et al., 2003). Hypothyroidism was induced by the anti-thyroid drug carbimazole, which is used in the treatment of human hyperthyroidism. (Deshpande et al., 2002). Spirulina (SP) is considered an excellent nutritional supplement with many health benefits. SP also contains phycocyanin, a powerful antioxidant which gives spirulina...
its rich green colour (Lissi et al., 2000). SP is well
documented for its clinical importance in diabetes,
hypertension, and cancer (Palaniswamy and Veluchamy,
2018), besides its antioxidant, immune-modulating, anti-
microbial (Finamore et al., 2017). Many woody plants,
including grape seeds and white pine, contain
proanthocyanidins (PAs), oligomers and polymers of
monomeric flavonoids. In comparison to vitamins C, E, and
-Carotene, PAs contained in (GSPE) exhibit much higher
protection against oxygen free radicals and possess a wide
range of biological, pharmacological, and chemo-protective
activities (Bagchi et al., 2002).
Several studies have shown that, by scavenging superoxide
and hydroxyl radicals, Proanthocyanins have strong
antioxidant and anticancer properties. They can also stop
drug-induced liver and kidney damage (Engelbrecht et al.,
2007). This study investigated the effect of experimental
hypothyroidism and hyperthyroidism on molecular
derangements and intracellular pathways alterations in the
thyroid and liver. Moreover, the possible protective effects
of spirulina and GSPE on thyroid dysfunction in rats were
explored.

2. MATERIAL AND METHODS

2.1. Experimental animals
A total 96 male rats, aged 8–12 weeks old and weighing
about 140–160 g. were employed in this investigation.
Separate wire mesh cages with good ventilation, humidity
control, and a 12-hour light/dark cycle was employed to
house the rats. Clean drinking water was available at all
times. Rats were separated for 15 days so they could
acclimatize before the trial started. The experimental protocols
were also approved by the Animal Care and Use Committee
at Benha University and are in accordance with the National
Institute of Health Guide for the Care and Use of Laboratory
Animals (Approval no. BUFVTM 02-8-21).

2.2 Chemical and Antioxidant agents
2.2.1. Chemicals
2.2.1.1. Thyroxine (Eltroxin)® 50 µg tablets, was
manufactured by GlaxoSmithKline GmbH (Germany). Rat
model of the hypothyroid received thyroxine at dose of (50,
100, 200 µg /kg b. wt.) orally for one, two and three weeks
of study, respectively (Guerrero et al., 1999)

2.2.1.2. Carbamazole;
Carbamazole (NeoMercazole® 5 mg tablets, was
manufactured by Amdipharm (Dublin, Ireland). Rat model
of the hypothyroid received carbamazole with a dose of 1.8
mg/kg b. wt./day administered orally over three weeks (Sakr
et al., 2012).

2.2.2. Antioxidant compounds
2.2.2.1. Spirulina platensis;
Pure Spirulina platensis powder was obtained from
(National Research Center–Dokki-Egypt). Dosage: rat 1.0
ml of a suspension of 300 mg/kg body weight of spray-dried
powder of spirulina platensis dissolved in distilled water
(Simsek et al., 2009).

2.2.2.2. Proanthocyanidin extract from grape seeds;
Grape Seed Proanthocyanidin (GSPE) was obtained from Al
Debeiki Pharma Company for Pharmaceutical industries
(AI Obour, Cairo, Egypt). DMSO 7 % was used to dissolve
the GSPE, and sterile saline solution was used to dilute it to
the right concentration. 150 mg/kg b.wt. of GSPE was used
as the dosage (Yousef et al., 2009).

2.3 Design of experiment:
Rats were split into two main experimental groups, housed
in individual cages, and classed as follows:

- Experiment A: Eltroxin- induced hyperthyroidism (50,
100, 200 µg /kg b. wt.) for first three weeks, respectively.
Hyperthyroidism experiment (A): six sets of rats were
used: Group 1 (control normal), Group 2
(hyperthyroidism) 50 µg /kg b. wt., Group 3 (GSPE
Protected): GSPE administered for the first 3 weeks and
continued with Thyroxine for another 3 weeks. Group 4
(GSPE treated): Thyroxine administered for 3 weeks,
followed by GPSE as in group 3. Group 5 (Spirulina
Protected): Spirulina and Eltroxin administration as in
group 3. Group 6 (Spirulina treated): Spirulina and
Eltrozin administration as group IV.

- Experiment B: carbimazole-induced hypothyroidism (1.8
mg/kg b. wt.). The administered GSPE dose (150 /kg
wt. /day) and Spirulina (300mg/kg b. wt./day) for 3 weeks.
Hypothyroidism experiment (B) rats divided also into 6
groups similar the above design in Hyperthyroidism
experiment (A) but carbimazole dose is stable (1.8 mg/kg
b. wt.) in the 3 weeks.

2.4 Sampling
Blood samples, liver tissue specimens were collected from
all Hyperthyroid and Hypothyroid animal groups 24 hours
after the last dose of GSPE and spirulina administrations.

2.4.1 Blood samples
Serum was isolated from blood samples by centrifugation
at 2500 rpm for 15 minutes after ocular vein punctures
were used to collect the blood samples. When used for the
later study of total cholesterol and triacylglycerols in the
experiments (A) and (B) were separated by an automatic
pipette, received in samples tubes, and preserved in a deep
freezer at -20 °C.

2.4.2. Tissue specimen
After being collected, the liver tissues were placed in
Eppendorf tubes, instantly frozen in liquid nitrogen, and
maintained at – 80 °C until RNA extraction for Bcl-2 and
caspase 8 determination in hyperthyroidism experiment (A)
andas well as PKCα, Micro- 224 and MicroRNA 382 gene
expression in hypothyroidism experiment (B).

2.5 Analysis
2.5.1. Biochemical analysis (Serum):
Serum total cholesterol and triacylglycerols were
determined by the methods of Ellefson and Caraway (1976)
and Stein (1987), respectively.

2.5.2. Molecular investigation (Liver):
Using real-time quantitative polymerase chain reaction
analysis (real-time qPCR), it was possible to identify the
miRNA expression levels of the liver Caspase-8, Bcl-2, and
PKC in the rat liver (Table 1). The load was managed with
β -actin. Following the manufacturer’s instructions, total
RNA was extracted from the heart using the High Kit for
extraction of pure RNA (Thermo Scientific, Fermentas,
#K0731) RNA Extraction kit. Revert Aid TM First Strand
CDNA synthesis kit (#EP0451, Thermo Scientific,
2020) was used to reverse transcribe each cDNA
sample. Then, real-time quantitative PCR amplification
was performed on Faststart Universal SYBR Green Master
(Roche, GER). The target gene was normalized with β-actin
by the 2-ΔΔCt method (Livak and Schmittgen, 2001).
miRNA224and miRNA382 were determined using real-time
PCR with SYBR Green and U6 as an internal control.
Thermo Scientific, USA, # K0221), a miRNA-specific forward primer (Table 2), and a universal reverse primer supplied with the Quanti-Mir RT kit were used to amplify the extracted cDNA in accordance with the manufacturer’s instructions.

Table 1 The forward and reverse primer sequences for qPCR primers.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Forward primer (5′→3′)</th>
<th>Reverse primer (5′→3′)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspase 8</td>
<td>CGGGAAGATCGACGAGTTA</td>
<td>CGCTCTGCAATTGTGAGG</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>ATGGCTTCTGTGGATCGATTAC</td>
<td>AGAGACAGCAGGAGAAAAATCAAAC</td>
</tr>
<tr>
<td>PKCα</td>
<td>TTTGTTACTTTCCTTCTGGTGCGGTT</td>
<td>ACATCTGTCCAGGGTGCCCA</td>
</tr>
<tr>
<td>β-actin</td>
<td>AAGCTGCTCCACCTGCGCAAAGGG</td>
<td>AGCCATGCTGTCACTCTTTCCC</td>
</tr>
</tbody>
</table>

Table 2 The forward and reverse primer sequences are utilized in qPCR.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer sequence (5′→3′)</th>
</tr>
</thead>
<tbody>
<tr>
<td>miRNA224</td>
<td>CAAGTCTCACTAGGTTGGTCGTT</td>
</tr>
<tr>
<td>miRNA382</td>
<td>GAAGTGTTCGTTGGTGGATTGC</td>
</tr>
<tr>
<td>U6</td>
<td>TGACACGCAATTCGTGGAGCGGTTC</td>
</tr>
<tr>
<td>Universal reverse primer</td>
<td>CCGAGTCAGGGTCGAGGTATTC</td>
</tr>
</tbody>
</table>

2.6. Statistical evaluation
All of the data were provided as Mean ± SEM. Duncan’s multiple range test was used to produce individual comparisons, and one-way analysis of variance (ANOVA) was used to assess statistical significance using SPSS 18.0 software in 2011. (DMRT). Values were deemed statistically significant when P ≤ 0.05.

3. RESULTS

3.1. Effect of Hyperthyroidism:
A notable reduction in serum total cholesterol and triacylglycerols concentrations was observed in Eltroxin induced hyperthyroidism at all doses. Treatment and protection with GSPE (G3 & G4), spirulina (G5 & G6) to hyperthyroid rats showed a noticeable rise in serum total cholesterol and triacylglycerols levels as compared hyperthyroid non treated group (Table 3 and Figures 1, 2).

![Fig. (1): Effect of Spirulina or GSPE treatment on serum total cholesterol concentration in experimental model of hyperthyroidism in rats.](image)

![Fig. (2): Effect of Spirulina or GSPE treatment on serum triacylglycerols concentration in experimental model of hyperthyroidism in rats.](image)

A significant upregulation in Caspase 8 and downregulation in Bcl-2 were observed in Eltroxin induced hyperthyroidism. Treatment and protection with GSPE (G3 & G4) and spirulina (G5 & G6) to Eltroxin induced hyperthyroidism in rats exhibited a significant down-regulation in Caspase 8 with upregulation in Bcl-2 as compared with hyperthyroid non treated group (Table 4 and Figures 3, 4).

3.2 Effect of hyperthyroidism:
A significant upregulation in miRNA 224 and PKCα and downregulation in miRNA 382 were observed in Carbimazole induced hyperthyroidism. Treatment and protection with GSPE (G3 & G4) and spirulina (G5 & G6) to Carbimazole induced hypothyroid rats exhibited a significant downregulation in miRNA 224 and PKCα with upregulation in miRNA 382 as compared with hyperthyroid non treated rats (Table 5 and Figures 5, 6 and 7).

4. DISCUSSION
A substantial drop in serum total cholesterol and triacylglycerols concentrations had been seen in Eltroxin-induced hyperthyroidism. Similarly, Lee et al. (2019) noted that TXN administration resulted in a considerable reduction in serum TC (total cholesterol) and TG (triacylglycerols) levels in the hyperthyroidism. Hyperthyroidism is in connection with reduced total and HDL cholesterol levels, as well as a lower total/HDL cholesterol ratio and apoA I levels. These effects are reversible if the underlying thyroid disorder is treated (O’Brien et al., 1997). Treatment and protection with GSPE or spirulina to hyperthyroid rats showed a considerable increase in serum total cholesterol and triacylglycerols levels as compared to hyperthyroid group. This outcome was consistent with Albrahim et al. (2020), who claimed that GSE treatment to Eltroxin-induced hyperthyroid mice for three weeks significantly normalize hyperthyroidism animals that reduced TC and TG levels while normalizing TSH levels that are already high. The major increase in serum TC and TG levels after treatment with Spirulina or GSPE, confirmed the anti-hyperthyroidism activity of GSPE and Spirulina. Moreover, Bolkiny et al. (2019) reported that in hypo- and hyperthyroid mice treated with costus root extract, their results showed a substantial improvement in serum cholesterol and triglycerides in hyperthyroid mice suggest that GSPE has the potential resistance against the negative role of TXN Inhibiting the factors that produce total cholesterol and triacylglycerols. A significant upregulation in Caspase 8 and downregulation in Bcl-2 were observed in Eltroxin-induced hyperthyroidism.
Table 3 Effect of protection and treatment with Spirulina or GSPE on serum total cholesterol and triacylglycerol concentrations of Eltroxin induced hyperthyroidism in rats.

<table>
<thead>
<tr>
<th>Animal groups</th>
<th>Total Cholesterol (mg/dl)</th>
<th>Triacylglycerols (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control non treated (G1)</td>
<td>94.17 ± 2.02^d</td>
<td>78.56 ± 1.80^d</td>
</tr>
<tr>
<td>Hyperthyroidism (G2)</td>
<td>53.09 ± 1.11^d</td>
<td>44.39 ± 1.06^d</td>
</tr>
<tr>
<td>Hyperthyroidism + GSPE protection (G3)</td>
<td>76.45 ± 1.63^c</td>
<td>60.05 ± 1.29^c</td>
</tr>
<tr>
<td>Hyperthyroidism + GSPE treatment (G4)</td>
<td>65.47 ± 1.39^b</td>
<td>53.80 ± 1.39^b</td>
</tr>
<tr>
<td>Hyperthyroidism + spirulina protection (G5)</td>
<td>84.04 ± 1.82^a</td>
<td>70.24 ± 1.73^a</td>
</tr>
<tr>
<td>Hyperthyroidism+ spirulina treatment (G6)</td>
<td>72.36 ± 1.55^b</td>
<td>55.71 ± 1.35^b</td>
</tr>
</tbody>
</table>

Data are presented as (Mean ± S.E). SE = Standard error. Mean values with different superscript letters in the same column are significantly different at (P≤0.05).

Table 4 Effect of protection and treatment with Spirulina or GSPE on liver Caspase 8 and Bcl-2 gene expression of Eltroxin induced hyperthyroidism in rats.

<table>
<thead>
<tr>
<th>Animal groups</th>
<th>Caspase 8 Fold change ± SEM</th>
<th>Bcl-2 Fold change ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control non treated (G1)</td>
<td>1.00 ± 0.08^e</td>
<td>1.00 ± 0.05^e</td>
</tr>
<tr>
<td>Hyperthyroidism (G2)</td>
<td>5.70 ± 0.22^a</td>
<td>0.12 ± 0.01^a</td>
</tr>
<tr>
<td>Hyperthyroidism + GSPE protection (G3)</td>
<td>3.39 ± 0.16^c</td>
<td>0.49 ± 0.02^b</td>
</tr>
<tr>
<td>Hyperthyroidism + GSPE treatment (G4)</td>
<td>4.50 ± 0.14^b</td>
<td>0.27 ± 0.01^d</td>
</tr>
<tr>
<td>Hyperthyroidism + spirulina protection (G5)</td>
<td>2.89 ± 0.10^c</td>
<td>0.59 ± 0.03^c</td>
</tr>
<tr>
<td>Hyperthyroidism+ spirulina treatment (G6)</td>
<td>3.41 ± 0.13^c</td>
<td>0.46 ± 0.02^c</td>
</tr>
</tbody>
</table>

Means within the same column carrying different superscript letters are significantly different (P≤ 0.05). SEM, Standard Error of Mean.

Table 5 Effect of protection and treatment with Spirulina or GSPE on liver miRNA 224, miRNA 382 and PKCα gene expression of Carbimazole induced hypothyroidism in rats.

<table>
<thead>
<tr>
<th>Animal groups</th>
<th>MirRNA 224 Fold change ±SEM</th>
<th>MirRNA 382 Fold change ±SEM</th>
<th>PKCα Fold change ±SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control non treated (G1)</td>
<td>1.00 ± 0.08^e</td>
<td>1.00 ± 0.06^a</td>
<td>1.00 ± 0.08^e</td>
</tr>
<tr>
<td>Hyperthyroidism (G2)</td>
<td>9.51 ± 0.42^a</td>
<td>0.06 ± 0.01^a</td>
<td>4.35 ± 0.18^a</td>
</tr>
<tr>
<td>Hyperthyroidism + GSPE protection (G3)</td>
<td>6.11 ± 0.28^a</td>
<td>0.51 ± 0.03^c</td>
<td>2.50 ± 0.12^a</td>
</tr>
<tr>
<td>Hyperthyroidism + GSPE treatment (G4)</td>
<td>7.57 ± 0.31^c</td>
<td>0.23 ± 0.01^d</td>
<td>3.41 ± 0.14^a</td>
</tr>
<tr>
<td>Hyperthyroidism + spirulina protection (G5)</td>
<td>2.99 ± 0.14^b</td>
<td>0.73 ± 0.04^d</td>
<td>1.83 ± 0.10^a</td>
</tr>
<tr>
<td>Hyperthyroidism+ spirulina treatment (G6)</td>
<td>6.19 ± 0.29^c</td>
<td>0.42± 0.02^c</td>
<td>2.60 ± 0.13^c</td>
</tr>
</tbody>
</table>

Means within the same column carrying different superscript letters are significantly different (P≤ 0.05). SEM, Standard Error of Mean.

Fig (3) Effect of Spirulina or GSPE treatment on liver caspase8 gene expression of experimental model of hyperthyroidism in rats.

Fig (4) Effect of Spirulina or GSPE treatment on liver Bcl-2 gene expression of experimental model of hyperthyroidism in rats.

Fig (5) Effect of Spirulina or GSPE treatment on liver miRNA 224 gene expression in experimental model of hypothyroidism in rats.

Fig (6) Effect of Spirulina or GSPE treatment on liver miRNA 382 gene expression in experimental model of hypothyroidism in rats.
The gene expressions of apoptotic mRNA, caspase-8 mRNA, and caspase-9 mRNA were substantially diminished and anti-apoptotic gene such as Bcl2 was significantly enhanced in the brain and liver of the fetuses after pregnant dams were orally administered with TXN. In some liver diseases, apoptosis results in the death of a considerable part of hepatocytes, impairing liver function. Hepatocyte damage may result in the production of apoptotic bodies and activation of Kupffer cells, which can in turn encourage inflammatory and fibrogenic responses (Hassa et al., 2018). Treatment and protection with GSPE or spirulina in Ektroxin-induced hyperthyroidism in rats exhibited a significant downregulation in Caspase 8 with upregulation in Bcl-2 as compared with hyperthyroid rats. This may be due to the fact that a mitochondria-mediated apoptotic pathway was found to link apoptosis to an increase in mitochondrial cytochrome c release, the Bax: Bcl-2 ratio, and caspase activation (Sharifi-Rad et al., 2021). Similarly, (Ebrahim, 2020) reported that the hippocampus of diabetic rats showed reduced oxidative stress and neuronal death in response to dietary spirulina or GSE’s antioxidant and/or anti-inflammatory properties. A major downregulated in Caspase-8 and upregulated in Bcl-2 were detected during treatment of TXN-induced DCM in rats with GSE and Spirulina (Sharifi-Rad et al., 2021). They have demonstrated a function in either controlling the activity and the level of expression of the apoptotic initiator of caspase-8 and other genes, including caspase-3, -9, Bax, Cytc, TNNI3, and NF-B genes to the lowest and upregulated the level of expression of Bcl2 gene (Ebrahim, et al., 2020).

A significant upregulation in mRNA 224 and PKCα and downregulation in mRNA 382 were observed in Carbimazole induced hypothyroidism. Treatment and protection with GSPE and spirulina to Carbimazole induced hypothyroid rats exhibited a significant downregulation in miRNA 224 and PKCα with upregulation in mRNA 382 as compared with hyperthyroid non treated rats. Carbimazole is well known for causing epigenetic modifications that hinder regular metabolism (Pisera-Fuster et al., 2020). As a result, the current study sought to evaluate the various miRNA epigenetic patterns associated with CMZ-induced hypothyroidism. Similarly, Peixoto et al. (2021) established that the miRNA 224 action results explained the long-term effects of early nicotine exposure (6 mg/Kg), which acts as a hypothyroidic agent like effector like Carbimazol (Alhowail et al., 2021). Also, Capriglione et al., (2022) investigated the profile of miRNAs including miR382-5p found in exosomes secreted in serum of 58 papillary thyroid cancer patients (PTC). Furthermore, (Eunjin et al., 2014; Nie et al., 2021) demonstrated that miR-382-5p directly targeted the 3-UTR of human NR1H4 mRNA and that its level was shown to be elevated in HCC tissues and to be inversely associated to NR1H4 mRNA levels utilizing a luciferase reporter experiment. Overexpression of miR-382-5p facilitated the malignant proliferative cycle of HCC cells by inhibiting the expression of FXR. Additionally, Tian et al., (2022) confirmed that administration of 2, 2'-dipyridyl disulphide that lowered thyroid hormone levels has significantly increased the gene expression of protein kinase C (pkc), here as the hormones decreased, the level of PKCα expression is increasing. Hypothyroidism raises the expression of Protein Kinase C, a regulator of cardiac contractility important in the myocardial cells' ischemia-reperfusion process. These processes explain hypothyroidism's resistance to ischemia-reperfusion, together with the inhibition of apoptotic c-Jun N-terminal Kinases (JNKs) (Pantostalim, 2008). In addition to McQuillin et al. (2007) showed that thyroid hormone specifically suppresses PKC and vice versa in the neonatal heart, as well as PKC in the adult heart. Changes in PKC caused by thyroid hormone are crucially permissive in the regulation of neurogenic responsiveness in ventricular cardiomyocytes. Lei et al. (2022) found that the wet and dry feed of Spirulina interestingly have a modulate on the PKCα. Collectively, the findings of this study clearly showed that the therapeutic properties of GSPE and Spirulina can modulate the upregulation of Caspase-8 in hyperthyroidism and the lowering of mRNA 244, PKCα in hypothyroidism, GSPE and Spirulina also enhancing the level of total cholesterol and triglycerides and Bcl-2 expression in hyperthyroidism as well as improving mRNA 382 in hypothyroidism, suggesting that they have multiple beneficial effects.

5. CONCLUSION

In conclusion, GSPE and Spirulina platensis had a potential therapeutic effect in thyroid dysfunction, through alleviating microRNA and PKCα that essential for thyroid hormone homeostasis and thyroid functions. Moreover, GSPE and Spirulina platensis mitigate liver damage and Thyroid disruptors via anti-apoptotic activities.

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