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تأثير المستخلص الكحولى للطحالب البنية على مضاعفات السمنة في الجرذان: دراسات عصبية ونسيجية

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Abstract:

The goal of the current investigation is to determine if treating an obese rat model's neurological and histological abnormalities with alcoholic brown algae extract can be beneficial. 36 rats were split into two primary groups: The first main group, consisting of six rats, was fed on a standard/basal diet (BD), while the second group (30 rats) was applied for diet-induced obesity (DIO) for eight weeks and divided into 5 sub-groups as follow: group (2), which was fed on BD just as a positive control (obese rats), and groups (3-6) which were fed on BD and given by oral gavages, via a feeding needle with 50, 100, 150, and 200 mg/kg bw/day ethanol extract of brown algae (Sargassum subrepandum) EEBA, respectively. Feeding normal rats on DIO causes them to weigh more than the normal group, have higher feed intake, and have a higher feed efficiency ratio (FER). During the 8-week trial, the BW, FI, and FER values of the healthy group were reported at 0.91%, 12.98 g/day/rat, and 0.075, respectively, but the obese group had higher rates of 57.14, 24.96, and 22.67%. After administering EEBA at doses of 50, 100, 150, and 200 mg/kg bw to feeding rats for eight weeks, the rats' BWG, FI, and FER significantly decreased ($p \leq 0.05$), their serum lipid profile variables improved, their neurological conditions (serotonin and dopamine levels and acetylcholine esterase action) improved, and their obesity-linked histological alterations in the adipose tissues and brain were positively manipulated. Every impact that EEBA had in obese rats was determined to be dose-dependent. These results establish a foundation for the application of EEBA in the management and prevention of obesity. Furthermore, the findings enhance the advantages of dietary modification and EEBA intervention in reducing obesity-related complications, such as neurological and histopathological problems.

Keywords:

Body weight, feed efficiency ratio, feed intake, serum lipid profile, acetylcholine esterase, dopamine, serotonin, adipose tissue, brain

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مستخلص البحث:

تهدف الدراسة الحالية إلى معرفة ما إذا كان التدخل الغذائى بالمستخلص الكحولي للطحالب البنية من شأنه أن يخفف من الاضطرابات العصبية والنسيجية في الفئران المصابة بالسمنة. لذلك، تم تقسيم ستة وثلاثين فأرًا إلى مجموعتين رئيسيتين، المجموعة الرئيسية الأولى (الضابطة، 6 فئران) تم تغذيتها على النظام الغذائي الأساسي/القياسى (BD) والمجموعة الرئيسية الأخرى (30 فأرًا) تم استخدامها لاحداث السمنة عن طريق التغذية على الوجبات الغذائية المحدثة للسمنة (DIO) لمدة 8 أسابيع وقسمت إلى خمس مجموعات فرعية على النحو التالي: المجموعة (2) التي تغذت على BD فقط كمجموعة ضابطة إيجابية (الفئران المصابة بالسمنة) والمجموعات (3-6) التي تتغذى على BD وتعطى عن طريق المكمقات الفموية باستخدام إبرة تغذية تحتوي على 50 و100 و150 و200 ملجم/كجم من وزن الجسم/يوم من مستخلص الإيثانول للطحالب البنيةEEBA (*Sargassum subrepandum*) ، على التوالي ولقد أظهرت النتائج إن تغذية الفئران السليمة على DIO يؤدي إلى زيادة وزن الجسم (BW) والمتناول من الغذاء (FI) ونسبة كفاءة التغذية (FER) مقارنة بالمجموعة الطبيعية .وفي نهاية التجربة (8 أسابيع) سجلت المجموعة الطبيعية قيما قدرها 0.91% و12.98 جرام/يوم/فأر و0.075 بالنسبة لـ BW و FIو PER بينما ارتفعت هذه القيم بمعدلات 57.14 و24.96 و22.67% في المجموعة التي تعاني من السمنة .أدى التدخل باستخدام 50، 100، 150، 200 ملجم/كجم من وزن الجسم) في تغذية الفئران لمدة 8 أسابيع إلى انخفاض ملحوظ (p≤0.05)في BWG و FIوFER، وتعزيز مقاييس صورة الدهون في الدم، وتخفيف الاضطرابات العصبية (محتوى الدوبامين والسيروتونين ونشاط أستيل كولين)، والتعامل بشكل إيجابي مع التغيرات النسيجية المرضية المرتبطة بالسمنة في الدماغ (المخ) والأنسجة الدهنية في الجرذان السمينة .أظهرت النتائج ان جميع التأثيرات المستحثة في الفئران السمينة بواسطة EEBA تعتمد على الجرعة المطبقة .توفر هذه النتائج أساسًا لاستخدام EEBA للوقاية من السمنة وعلاجها .كما تدعم البيانات فوائد تعديل النظام الغذائي، والتدخل بـ EEBA ، في التخفيف من المضاعفات المرتبطة بالسمنة بما في ذلك الاضطرابات العصبية والنسيجية.

الكلمات المفتاحية:

وزن الجسم، الكمية المتناولة من الغذاء، نسبة كفاءة التغذية، مستوى الدهون في الدم، انزيم الأسيتيل كولين استريز، الدوبامين، السيروتونين، الأنسجة الدهنية، المخ.

Introduction

A complicated condition known as obesity is brought on by a disturbance in the balance of the body's energy causing an extra mass of adipose tissue (Nammi *et al.,* 2004). Hereditary, physiological, environmental, dietary, physical activity, and exercise decisions all contribute to it. Body mass index (BMI), which is estimated as kilograms of weight divided by squared meters (kg/m2) of height, is a regularly utilized metric to determine the prevalence of obesity (Taylor et al., 1998). Obesity can be described as a BMI of 30 kg/m2 or above. Obesity results in around 4.7 million preventable deaths worldwide annually. It accounted for 12.3% of all deaths globally and 8.4% of all disability-adjusted life years (DALYs) lost to non-communicable diseases, placing it as the fifth most prevelant avoidable cause of death (Felisbino-Mendes, 2020 and Mehrzad, 2020). According to Ramasamy et al. (2019), the various consequences of obesity have been linked to a significant portion of health care costs. They also cause extra financial burdens on national budgets due to decreased worker productivity, a rise in disability, and early death of humans. These issues arise from the correlation between obesity and many illnesses, involving obstructive sleep apnea, cardiovascular disease, some cancers, type 2 diabetes, osteoarthritis, asthma, and immunological and neurological conditions (Caterson, 2009; Elhassaneen and Salem, 2014; Alexopoulos *et al.,* 2016; Elmaadawy et al., 2016; Mehram et al., 2021; Shalaby and Elhassaneen, 2021; Elhassaneen et al., 2019, 2020-a, 2022 a and b; 2023 a and b; Boraey, 2023). Additionally, high blood sugar levels, insulin resistance, elevated triglycerides levels, elevated serum cholesterol levels, and hypertension, are among the metabolic syndrome problems that obesity has been linked to (Ka et al., 2009; Grundy, 2004 and Elhassaneen et al., 2020-b; 2022-a). According to Cheng et al. (2014), these conditions appear to be linked to adipokine dysregulation, glucotoxicity, lipotoxicity, and chronic inflammation.

For the reasons mentioned above, several pharmacological methods have been researched recently for ways to treat or prevent obesity. Nonetheless, only a minority of these methods have been produced as acceptable and effective pharmaceutical products (Jandacek and Woods, 2004). Furthermore, the modern pharmaceutical treatment is expensive and linked to a number of adverse reactions that lead people to quit taking their medications. Therefore, it was imperative to look for other options, especially those derived from natural sources because they are less expensive and have less adverse reactions. Thus, a variety of plant materials have been used to create crude medications, including extracts, powders, and other herbal remedies that have shown promise in treating and/or preventing obesity and its consequences in laboratory animals (Elhassaneen et al., 2018; Mahran et al., 2018; Elhassaneen et al., 2019; Elhassaneen et al., 2020 c-d; Shalaby and Elhassaneen, 2021 and Elhassaneen et al., 2022 a and b; Boraey, 2023; Gadall, 2023). The findings

of these investigations served as a major motivator for further investigations in this area, utilizing various plant components which are widely available in both local and worldwide settings.

The broad family of marine multicellular algae called brown algae (Family Phaeophyceae) includes a variety of seaweeds found in various nations, involving Egypt. For food and habitat, many humans are also familiar with some forms of brown algae. In contrast to this, brown algae are part of a wide and varied world of algae that are vital to our survival as well as helpful to it (Guiry, 2001). Although the abundance of herbivorous predators, brown algae are also commonly found as the predominant vegetation in shallow water subtropical and tropical ecosystems in Egypt (Gerwick et al., 1981). Brown algae are now the most common category in the littoral zone along the Egyptian coast. In the waters of the Mediterranean and Red Seas, certain species, as those owing to the Sargassum genus, form distinctive floating seaweed mats that act as homes for numerous species (Mann and Martin, 2002; Rushdi et al., 2020). They are significant for commercial application since they are now the focus of in-depth research on their own (El-Gamal, 2020; Elhassaneen et al., 2020 and 2023-a; Rushdi et al., 2020; Fayez, 2021; Gad Alla, 2023). Such studies indicated that brown algae are great suppliers of numerous nutrients and bioactive materials such as lipids, proteins, minerals, fibers, essential amino, fatty acids, phenolics, polysaccharides, alkaloids, carotenoids, terpenoids etc. These investigations additionally demonstrated that these components reveal a variety of biological properties, like scavenging and antioxidant effects, lipid oxidation inhibition, antifungal and antibacterial properties, and high nutritional value. Thus, brown algae have the potential to treat diabetes, hyperlipidemia/hypercholesterolemia, tuberculosis, liver diseases, obesiy, cancer, osteoporosis and aging diseases (Kanke et al., 1998; Funahashi et al., 2001; Lawson, 2001; El-Gamal, 2020; Elhassaneen et al., 2023-a; Rushdi et al., 2020; Fayez, 2021; Gad Alla, 2023). Also, several of such investigations have investigated the protective impact of brown algae on various obesity sequaele like hyperglycemia, serum lipid profile, atherosclerosis, heart disorder, kidney and liver functions in human and rat model. However, there is currently a deficiency of knowledge on the impact of consuming plant parts, such as brown algae, on the neurological consequences of obesity. This work was carried out to assess if treating neurological and histological problems in an obese rat model with ethanol extract of brown algae (Sargassum subrepandum) (EEBA) may close this knowledge gap. Additionally, the bioactive materials and the biological properties of brown algae genus Sargassum found on the shores of Mediterranean Sea in Egypt will fall in the objective of this study.

Materials and Methods

Materials

Brown algae samples

Samples of brown algae (Sargassum subrepandum) were gathered from the Mediterranean Sea coastlines of Alexandria, Alexandria Governorate, Egypt. After being removed from the water, the specimens were examined by staff members at the Faculty of Agriculture, Alexandria University, Alexandria, Egypt.

Chemicals and Machines

Morgan for Chemical Industries in Cairo, Egypt was the source of casein procurement. All additional chemicals (except from those specifically mentioned), reagents, and solvents were gathered from El-Ghomhorya Company for Trading Medicines, Chemicals, and Medical Instruments in Cairo, Egypt, and were of analytical quality. The kit was acquired from BIODIAGNOSTIC, Dokki, Giza, Egypt, and included tests for the blood lipid profile (high density lipoprotein cholesterol, HDL-c; total cholesterol, TC; and triglycerides, TGs). Utilizing the UV-160A; Shimadzu Corporation, Kyoto, Japan, absorbance for several assays was determined over the course of this investigation.

Methods

Preparation of brown algae powder and extracts

Brown algae extracts and powder were made based on the procedure illustrated by Abd Elalal et al. in 2021. To put it briefly, brown algae samples were manually cleaned, sorted, and dried until the final product had around 8% moisture. The dehydrated samples were finely powdered, and the portion that made it through an 80 mesh filter was saved for usage in the manufacture of extracts and analysis. Twenty grams of dry brown algae powder and 180 milliliters of water were homogenized, then put in a beaker and shaken at 200 rpm in an orbital shaker (Unimax 1010, Heidolph Instruments GmbH & Co. KG, Germany) for a full hour at room temperature in order to prepare the extracts. A rotary evaporator was utilized to extract the remaining solvent at low pressure and 45°C.

Animals

36 mature male albino rats of the Sprague Dawley strain, weighing between 140 and 150 g apiece, were acquired from the Ministry of Health and Population at Helwan Station in Helwan, Cairo, Egypt, for usage in this investigation.

Animal diets

As stated by (AIN, 1993), the base diet is made up of the following ingredients: corn oil (10%), protein (10%), mineral mixture (4%), methionine (0.3%), choline chloride (0.2%), vitamin mixture (1%), cellulose (5%), and corn starch (69.5%) that remains over. Research Diets, Inc., NJ, prepared the diet-induced

obesity (DIO) using the following ingredients: L-cystine (0.35%), casein (23.3%), sucrose (20.14%), maltodextrin (11.65%), corn starch (8.48%), calcium carbonate (0.64%), soybean oil (2.91%), mineral mixture (1.17%), lard fat (20.69%), dicalcium phosphate (1,52%), and potassium citrate. 1 H2O (1.92%), vitamin combination (1.17%), and bitartrate of choline (0.23%). Recipes for vitamin mix (Table 1) and salt combinations (Table 1) were created in the manner described by Reeves et al. (1993).

Experimental design

Every experiment complies with the National Research Council's (NRC, 1996) Institute of Laboratory Animal Resources, Commission on Life Sciences guidelines. A total of thirty-six rats weighing between 140 and 150 grams each were maintained in a room separately in wire cages with a temperature of 27 ± 5 0C, relative humidity of 55 ±5%, a 12-hour lighting cycle, and other standard, standard circumstances. Prior to the study; each rat was fed a baseline diet (BD) for 7 days in order to allow them to get acclimated. Following a one-week duration, 36 rats were split into two primary groups: The first main group, consisting of six rats, was fed on a standard/basal diet (BD), while the second group (30 rats) was applied for diet-induced obesity (DIO) for eight weeks and divided into 5 sub-groups as follow: group (2), which was fed on BD just as a positive control (obese rats), and groups (3-6) which were fed on BD and given by oral gavages, via a feeding needle with 50, 100, 150, and 200 mg/kg bw/day ethanol extract of brown algae (Sargassum subrepandum) EEBA, respectively. According to a number of the findings from earlier research, EEBA extract doses were chosen for the trials (Elhassaneen et al., 2021 and 2023; Fayez, 2021; Gadall, 2023). For eight weeks, every group mentioned above was housed in a separate cage. Rats were weighed at the start of the experiment, once a week, and at the completion of the trial.

Biological evaluation

Throughout the trial duration (56 days), the body weight was observed weekly and the diet was documented daily. In accordance with Chapman et al. (1959), food efficiency ratio (FER), the food intake (FI), and body weight gain (BWG, %) were measured utilizing these equations: BWG (%) is equal to (Final weight - Initial weight)/Initial weight×100, while FER is equal to grams of body weight increase (g/56 days) divided by grams of feed intake (g/56 days).

Blood sampling

Rats were scarified under ethyl ether anesthesia at the end of the trial duration, following a twelve-hour fast, and blood samples were taken from the abdominal aorta of the rats.

Hematological analysis

Blood lipid profile

The blood levels of total cholesterol (TC), HDL-cholesterol, and triglycerides (TGs) were assessed using the techniques described by Richmod (1973), Lopes-Virella et al. (1977), and Fossati and Prenape (1982), respectively. The following formula, developed by Fniedewald et al. (1972), was utilized to assess low density lipoprotein cholesterol (LDL-c): LDL-c = TC – (HDL-c + TGs/5).

Level of Dopamine and serotonin

The methods of Mitra and Guha (1989) and Mahood and Hamzah (2010) were utilized to evaluate the levels of serotonin and dopamine in serum, respectively.

Acetylcholinestrase (AChE) determination

AChE activity in serum was evaluated using Gowenlock's colorimetric approach (1988) and expressed as Rappaport units/mL.

Histopathological Examination

After the rats were sacrificed, sections of the internal organs (kidneys, lungs, heart, liver, spleen, and brain) were extracted and placed in 10% neutral buffered formalin. Following trimming and dehydration in increasing alcohol grades, the preserved specimens were cleaned in xylene, sectioned (4-6 µm thick), embedded in paraffin, stained with hematoxylin and eosin, and viewed under a microscope (Carleton, 1978).

Statistical Analysis

Results were measured by utilizing Microsoft Excel Software (version 15.0, 2013) and expressed as means ± SD with. The Student t-test and the statistical software MINITAB 12 (Minitab Inc., State College, PA) were utilized to evaluate the data statistically. Statistical significance was determined with a P-value of ≤ 0.05.

Results and Discussion

Effect of intervention with ethanol extract of brown algae (EEBA) on body weight (BW), feed intake (FI) and feed efficiency ratio (FER) of obese rats

Table (1) and Figures (1 and 2) depict the effects of the ethanol extract of brown algae (EEBA) intervention on the feed intake (FI), body weight (BW), and feed efficiency ratio (FER) of obese rats. Based on these findings, it can be shown that feeding rats on DIO (control +) causes the BWG, FI, and FER to rise compared to the normal group. Rats in the healthy group reported BW, FI, and PER values of 0.91%, 12.98 g/day/rat, and 0.075 at the completion of the 8-week trial; in the obese group, these values grew at rates of 57.14, 24.96, and 22.67%. After feeding rats EEBA at doses of 50, 100, 150, and 200 mg/kg bw for eight weeks, the BWG, FI, and FER of the

obese rats declined considerably ($p \leq 0.05$) at rates of 52.75, 41.76, 25.27, and 19.78%, 21.73, 16.41, 10.40, and 7.16%, and 21.73, 16.41, 10.40, and 7.16%, respectively. The rate at which the obese rats' BWG, FI, and FER decreased was shown to be dose-dependent. Elhassaneen et al. (2022) observed a similar tendency after using brown algae extract (Sargassum subrepandum) at high concentrations (i.e., 0.25 to 1.0% w/w) in the intervention procedure. Furthermore, following 4 weeks of feeding, Maeda et al. (2008) showed that supplementing the rat's diet with brown algae powder resulted in a substantial ($p \leq 0.05$) decline in white adipose tissue. In the same setting, Elhassaneen et al. (2020-a) discovered that adding brown algae powder to rats' diets at a rate of 1 to 4% resulted in a significant ($p \leq 0.05$) decline in the model obese rats' body weight. Data from this study along with others demonstrated that EEBA's beneficial effects on the management of obesity would be linked to the great concentration of various bioactive component classes it includes, such as dietary fiber, carotenoids, tannins, anthocyanins, polyphenols, flavonoids, terpenoid, triterpenoids, and polysaccharides (El-Gamal, 2020; Elhassaneen et al., 2020-a, 2021, 2023; Gadall, 2023). One or more of these functions might best describe the potential methods by which these bioactive chemicals aid in the prevention or treatment of obesity: 1) the capability of these components and their metabolites to initiate multiple roles, which play a role in regulating their effect in adipocyte function and subsequent obesity, 2) the up-regulation of mitochondrial uncoupling protein 1 that can raise resting energy use, 3) the inhibition of adipocyte differentiation and accumulation of lipids, 4) these substances may interact with a number of transcription parameters owing to the nuclear receptor superfamily which are linked to reactions to inflammation and oxidative stress, scavenging free radicals and preventing the oxidation of lipids, additionally 5) Dietary fiber can assist in avoiding obesity and its associated diseases by helping to give stool bulk, facilitating transit via the digestive tract, and encouraging the development of gut flora (Maeda et al., 2008; Kim and Lee, 2012; Elmaadawy et al., 2016; Ruheea and Katsuhiko, 2018; Elbasouny et al., 2019; Elhassaneen et al., 2016 and 2023; Gadall, 2023).

Table 1. Effect of intervention with ethanol extract of brown algae (EEBA) on body weight (BW), feed intake (FI) and feed efficiency ratio (FER) of obese rats

Value	Control (-) Normal	Control (+) Obese	EEBA intervention (mg/kg bw)			
			50	100	150	200
Body weight gain (BWG, %)						
Mean	0.91[d]	1.43[a]	1.39[a]	1.29[b]	1.14[bc]	1.09[c]
SD	0.03	0.09	0.08	0.11	0.06	0.05
% of Change	0.00	57.14	52.75	41.76	25.27	19.78
Feed intake (FI, g/day/rat)						

Mean	12.98 [c]	16.22 [a]	15.80 [a]	15.11 [ab]	14.33 [b]	13.91 [bc]
SD	0.74	0.93	0.73	1.23	0.67	0.79
% of Change	0.00	24.96	21.73	16.41	10.40	7.16
Feed efficiency ratio (FER)						
Mean	0.075 [c]	0.092 [a]	0.090 [ab]	0.084 [b]	0.080 [b]	0.080 [bc]
SD	0.009	0.012	0.011	0.007	0.010	0.008
% of Change	0.00	22.67	20.00	12.00	6.67	6.67

Each value represents mean of six rats. At P≤0.05, significant differences are explained by means in the same column with distinct superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

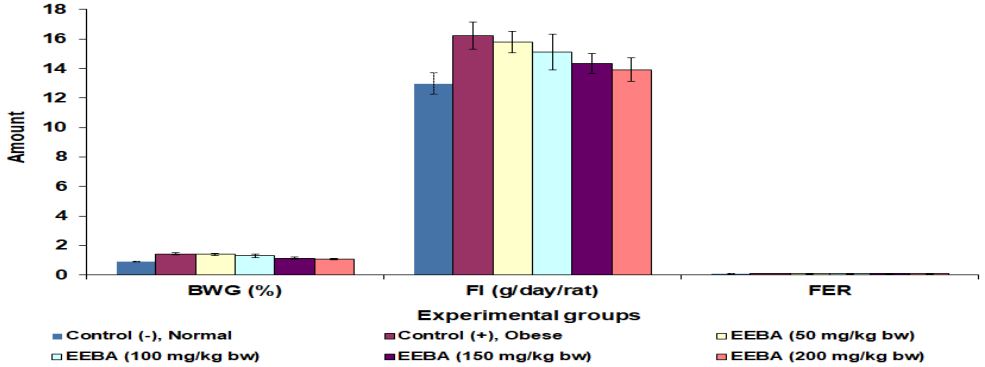

Figure 1. Effect of a dietary intervention with ethanol extract of brown algae (EEBA) on body weight (BW), feed intake (FI) and feed efficiency ratio (FER) of obese rats

Each value represents mean of six rats. At P≤0.05, significant differences are explained by means in the same column with distinct superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

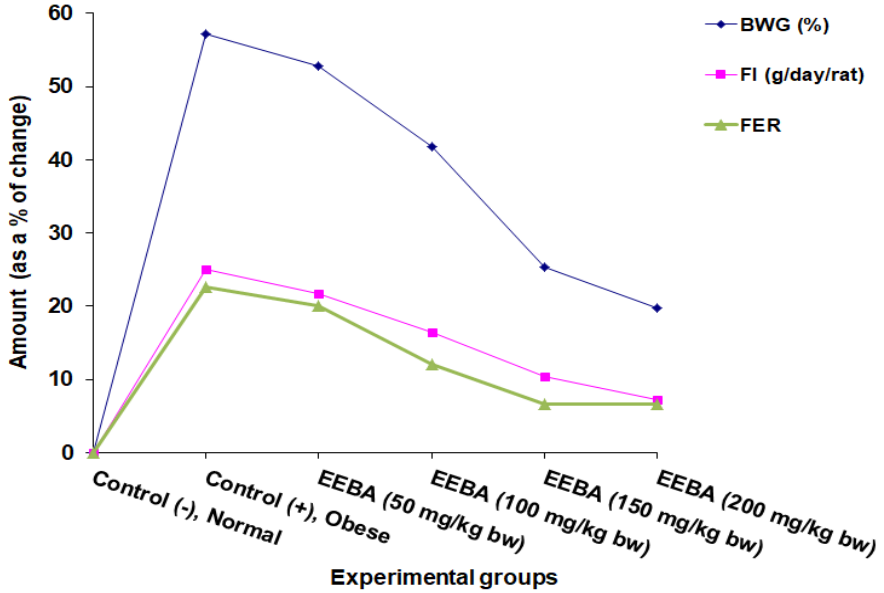

Figure 2. Effect of a dietary intervention with ethanol extract of brown algae (EEBA) on body weight (BW), feed intake (FI) and feed efficiency ratio (FER) (as a % of change) of obese rats

Each value represents mean of six rats. At P≤0.05, significant differences are explained by means in the same column with distinct superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on weight organs of obese rats

Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on weight organs of obese rats is revealed in Figures (2 and 3) and Table (2). Based on these findings, it can be shown that feeding rats DIO (control +) leads to their organ weight to rise relative to the healthy group. Rats in the normal group reported values for the kidneys, liver, spleen, lungs, heart, and brain at the conclusion of the 8-week trial, which were 1.31, 4.82, 0.66, 1.29, 0.61, and 1.58 g. In the obese group, these values grew at rates of 17.13, 6.19, 6.68, 4.59, 14.51, and 8.07%. Rats fed EEBA at doses of 50, 100, 150, and 200 mg/kg bw for eight weeks revealed a substantial ($p \leq 0.05$) decline in the organs of the obese rats, although at various rates. The rate at which the obese rats' organ weight decreased was shown to be dose-dependent. These findings correspond with what other writers have documented (Elhassaneen et al., 2023-a; Gadall, 2023). Also, Boraey (2023) and Elhassaneen et al., (2023-b) recorded the same observation with other plant parts i.e. Ashwagandha (Withania somnifera L.) roots contains almost the same bioactive compounds. Mandal et al. (2012) stated that in population studies, organ weights increased statistically significantly with body mass index (BMI).

Table 2. Effect of a dietary intervention with ethanol extract of brown algae (EEBA) on weight organs of obese rats

Value	Control (-) Normal	Control (+) Obese	EEBA intervention (mg/kg bw)			
			50	100	150	200
			Liver (g)			
Mean	4.82 ^{c}	5.11 ^{a}	5.08 ^{a}	5.09 ^{a}	4.94 ^{b}	4.90 ^{bc}
SD	0.22	0.32	0.19	0.21	0.13	0.33
% of Change	0.00	6.19	5.37	5.61	2.63	1.66
			Kidneys (g)			
Mean	1.31 ^{d}	1.54 ^{a}	1.51 ^{a}	1.51 ^{a}	1.45 ^{b}	1.37 ^{c}
SD	0.09	0.11	0.08	0.08	0.07	0.11
% of Change	0.00	17.13	14.88	14.88	10.61	4.49

Spleen (g)						
Mean	0.66 [b]	0.70 [a]	0.69 [a]	0.68 [a]	0.68 [a]	0.67 [ab]
SD	0.02	0.04	0.02	0.08	0.09	0.05
% of Change	0.00	6.68	4.51	3.05	3.05	1.53
Heart (g)						
Mean	0.61 [b]	0.69 [a]	0.69 [a]	0.67 [ab]	0.64 [b]	0.63 [b]
SD	0.02	0.06	0.02	0.04	0.02	0.03
% of Change	0.00	14.51	12.90	9.64	4.84	3.22
Lungs (g)						
Mean	1.29 [b]	1.35 [a]	1.35 [a]	1.34 [a]	1.31 [ab]	1.31 [ab]
SD	0.06	0.01	0.11	0.06	0.10	0.07
% of Change	0.00	4.59	4.59	3.77	1.51	1.51
Brain (g)						
Mean	1.58 [b]	1.70 [a]	1.69 [a]	1.67 [ab]	1.62 [b]	1.60 [b]
SD	0.09	0.11	0.12	0.09	0.17	0.07
% of Change	0.00	8.07	7.44	6.21	3.11	1.86

Every value represents mean of six rats. At P≤0.05, significant differences are explained by means in the same column with distinct superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

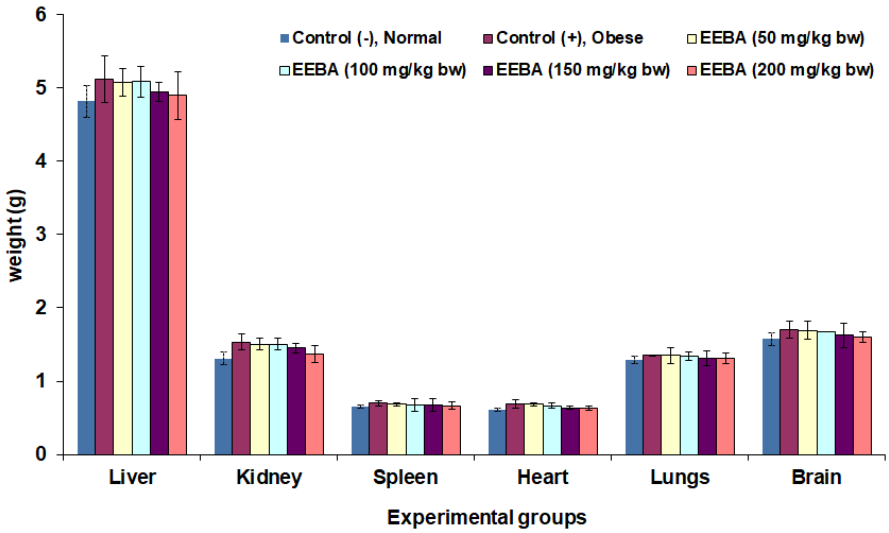

Figure 3. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on weight organs of obese rats

Every value represents mean of six rats. At P≤0.05, significant differences are explained by means in the same column with distinct superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

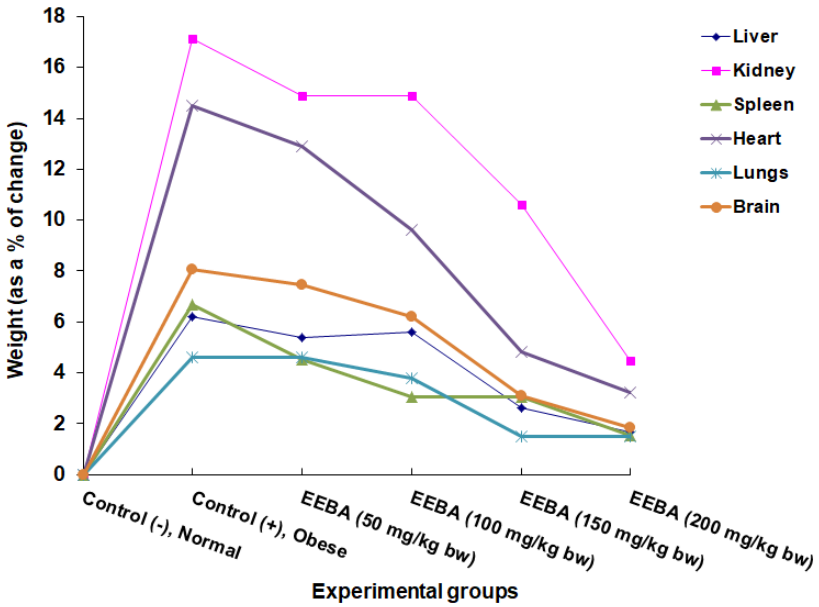

Figure 4. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on weight organs (as a % of change) of obese rats

Every value represents mean of six rats. At P≤0.05, significant differences are explained by means in the same column with distinct superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on serum lipids profile concentration of obese rats

Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on concentration of serum lipids profile of obese rats was revealed in Table (3) and Figures (2 and 3). Depending on these findings, it was observed that TG, TC, LDL-c, and VLDL-c elevated significantly ($p \leq 0.05$) in relation to the healthy control group by 49.96, 69.24, 184.04, and 49.96%, respectively. The HDL showed a -22.32% decline, demonstrating contrary to the pattern. The administration of EEBA at doses of 50, 100, 150, and 200 mg/kg bw led to a great ($p \leq 0.05$) improvement in the serum lipid profile by reducing the levels of TC, TG, LDL-c, and VLDL-c at varying rates. The current research illustrated the positive impacts of EEBA in enhancing the serum lipid profile brought on by obesity. The high concentration of bioactive chemical classes in EEBA, such as flavonoids, polyphenols, terpenoid, triterpenoids, polysaccharides, tannins, carotenoids, anthocyanins, kaempherol, and fiber, may be responsible for this biological effect. These findings correspond with the observations made by other writers (Elhassaneen et al., 2023-a; Gadall, 2023). Furthermore, a number of investigations have shown that the same behavior with plant portions that contain the same bioactive substances as before improves the blood lipid profile in rats that are obese (Elhassaneen, et al., 2018; El-Harbi, 2018; Emam et al., 2018; Elbasouny et al., 2019; Elhassaneen et al., 2019; Elhassaneen et al., 2020; Almutairiu, 2020; Alqallaf, 2021; Ehassaneen et al., 2023-b; Boraey, 2023). Numerous researchers found in a population research that obese or overweight individuals and who lose weight for a moderate amount of time (5–10 kg) have lower levels of TC, TG, and LDLP and higher levels of HDL (Christensen et al., 2007; Bales and Buhr, 2008; Elhassaneen ad Salem, 2014). In general, heart diseases are major health problem all over the world involving Egypt. Serum raised concentrations of TG, TC and LDL-c in addition to decreased HDL in the blood are great risk factors for heart diseases (Bedawy, 2008). The way food is consumed has a significant impact on how the blood's lipid profile is managed. Previously, the initial objective of dietary treatment to minimize the risk of cardiac illnesses has been to reduce the consumption of cholesterol and saturated fat. In addition, a number of dietary elements and phytochemicals, including those in EEBA, have been linked to hypocholesterolemia. The results of this investigation suggested that the identified bioactive chemicals in EEBA may have a lot of biological roles, involving scavenging, antioxidant, and anti-inflammatory properties, in addition to inhibiting lipid oxidation, which might enhance serum lipid profile (Kuhlmann et al., 1998, El-Harbi, 2018; Emam et al., 2018; Kashaf, 2018; Abd Elalal et al., 2021; Ehassaneen et al., 2023-b; Boraey, 2023). Additional substances like fiber, which makes up the majority of brown algae, are crucial in reducing the negative effects of obesity, particularly its consequences on the blood lipid profile. In light of this, Camire et al.

(1993) and Elbasouny et al. (2019) observed that one way specific dietary fiber sources reduce plasma cholesterol is through the ability of fibers to bind bile acids.

Table 2. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on serum lipid profile of obese rats

Value	Control (-) Normal	Control (+) Obese	EEBA intervention (mg/kg bw)			
			50	100	150	200
Triglycerides (TG, mg/dL)						
Mean	86.75 ^{d}	130.09 ^{a}	124.95 ^{ab}	110.21 ^{b}	101.19 ^{c}	94.57 ^{cd}
SD	4.02	9.56	8.17	5.69	3.98	8.19
% of Change	0.00	49.96	44.03	27.05	16.64	9.01
Total cholesterol (TC, mg/dL)						
Mean	117.0 ^{e}	198.03 ^{a}	192.00 ^{ab}	178.43 ^{b}	151.68 ^{c}	139.31 ^{d}
SD	9.87	15.05	16.00	8.87	7.65	10.20
% of Change	0.00	69.24	64.09	52.49	29.63	19.06
High density lipoprotein- cholesterol (HDL-c, mg/dL)						
Mean	53.82 ^{a}	41.81 ^{c}	42.84 ^{c}	44.76 ^{bc}	48.00 ^{b}	49.98 ^{ab}
SD	5.03	4.99	2.95	3.72	7.18	6.34
% of Change	0.00	-22.32	-20.41	-16.83	-10.82	-7.14
Low density lipoprotein- cholesterol (LDL-c, mg/dL)						
Mean	45.84 ^{e}	130.20 ^{a}	124.17 ^{ab}	111.62 ^{b}	83.44 ^{c}	70.42 ^{d}
SD	3.46	10.45	10.67	9.21	5.37	4.23
% of Change	0.00	184.04	170.88	143.50	82.03	53.63
Very low density lipoprotein- cholesterol (VLDL-c, mg/dL)						
Mean	17.35 ^{c}	26.02 ^{a}	24.99 ^{ab}	22.04 ^{b}	20.24 ^{bc}	18.91 ^{c}
SD	2.02	1.84	3.09	2.49	1.43	2.25
% of Change	0.00	49.96	44.03	27.05	16.64	9.01

Every value represents mean of six rats. At $P \leq 0.05$, a significant difference is explained by means in the same column using various superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

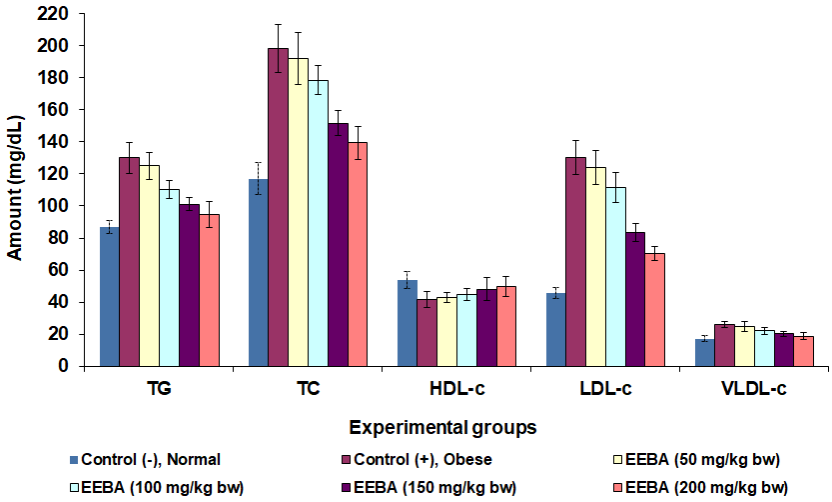

Figure 5. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on serum lipid profile of obese rats

Every value represents mean of six rats. At P≤0.05, a significant difference is explained by means in the same column using various superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

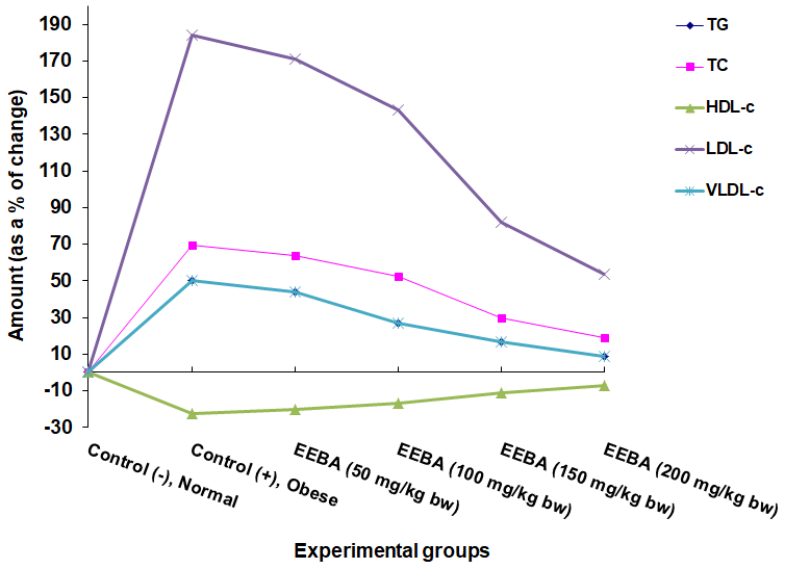

Figure 6. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on serum lipid profile (as a % of change) of obese rats

Every value represents mean of six rats. At P≤0.05, a significant difference is explained by means in the same column using various superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

Impact of intervention with ethanol extract of brown algae (EEBA) on neurological disorder of obese rats

Serum acetylcholine esterase (AChE) activity

Data in Figures and Tables (2 and 4) are revealed the impact of dietary intervention with ethanol extract of brown algae (EEBA) on acetylcholine esterase of obese rats.

Table 5. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on acetylcholine esterase (ACE, Rappapor U/mL) of obese rats

Value	Control (-) Normal	Control (+) Obese	EEBA intervention (mg/kg bw)			
			50	100	150	200
Mean	76.78 [d]	94.29[a]	93.38 [a]	90.72 [a]	84.55 [b]	80.47 [c]
SD	6.42	8.11	5.02	7.33	5.31	6.73
% of Change	0.00	22.80	21.62	18.15	10.11	4.80

Every value represents mean of six rats. At P≤0.05, a significant difference is explained by means in the same column using various superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

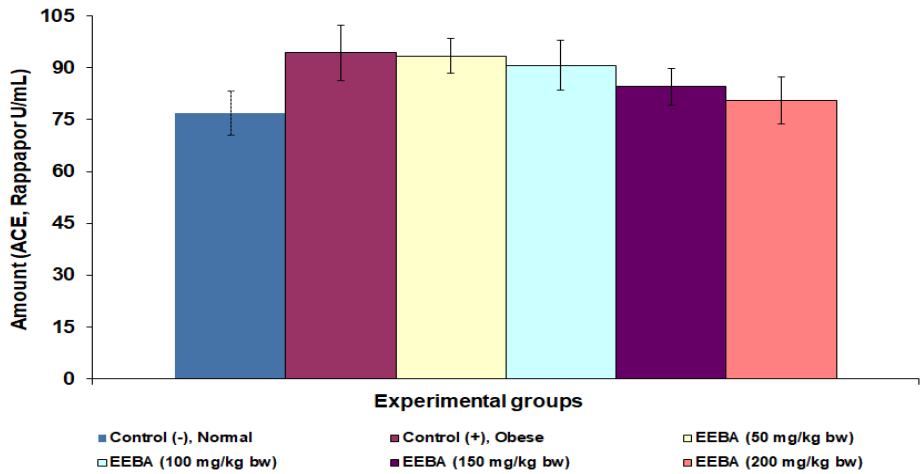

Figure 9. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on acetylcholine esterase (ACE, Rappapor U/mL) of obese rats

Every value represents mean of six rats. At P≤0.05, a significant difference is explained by means in the same column using various superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

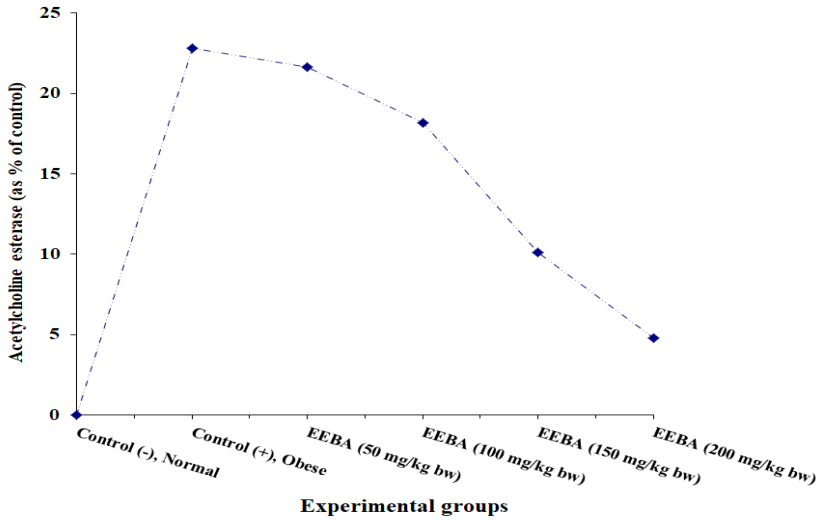

Figure 9. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on acetylcholine esterase (as a % of change) of obese rats

Every value represents mean of six rats. At P≤0.05, a significant difference is explained by means in the same column using various superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

Serum neurotransmitters (serotonin and dopamine)

Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on serum serotonin and dopamine of obese rats are revealed in Figures (5 and 7) and Table (4). These data allowed for the observation that obesity resulted in a significant (p≤0.05) decreasing in serum dopamine and serotonin by the rate of -14.30 and -12.93% in comparison to the healthy group. After eight weeks of feeding rats with EEBA at doses of 50, 100, 150, and 200 mg/kg bw, the levels of dopamine and serotonin substantially (p≤0.05) elevated in comparison to the healthy group, recording -12.75, -11.50, -8.10, and -4.98% and -10.78, -9.49, -5.05, and -2.33%, respectively. Dopamine and serotonin levels decreased at a rate that was dose-dependent.

Table 6. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on serum serotonin and dopamine of obese rats

Value	Control (-) Normal	Control (+) Obese	EEBA intervention (mg/kg bw)			
			50	100	150	200
	Dopamine (pg/ml)					
Mean	92.64 [a]	79.39 [b]	80.83 [b]	81.99 [b]	85.13 [ab]	88.02 [a]
SD	8.31	6.04	4.45	8.56	5.13	4.75

% of Change	0.00	-14.30	-12.75	-11.50	-8.10	-4.98
			Serotonine (ng/ml))			
Mean	218.37 [a]	190.14 [c]	194.83 [c]	197.64 [c]	207.35 [b]	213.28 [a]
SD	10.40	15.67	10.67	9.90	8.56	16.08
% of Change	0.00	-12.93	-10.78	-9.49	-5.05	-2.33

Every value represents mean of six rats. At $P \leq 0.05$, significant differences are explained by means in the same column with distinct superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

AChE is a cholinergic enzyme, which is generally situated in postsynaptic neuromuscular junctions, especially in nerves and muscles. Acetylcholine (ACh) is a naturally found neurotransmitter that is hydrolyzed by AChE into choline and acetic acid instantly. Choline helps lipids enter cells and keeps them from accumulating in the liver. As a result, AChE is recognized to be involved in the cholinergic response's termination. Both muscarinic and nicotinic receptors are overstimulated throughout a cholinergic crisis, which causes a significant parasympathetic reaction that includes bradycardia, memory deficits [Alzheimer's disease], elevated gastric motility (diarrhea), weakness/paralysis, cramping in the muscles, and excessive secretions (Bartus et al., 1982; Craig et al., 2011). Moreover, memory impairments and oxidative stress were caused by elevated AChE activity in the brain (Melo et al., 2003). Data from this study along with others most probably illustrate the mechanism of EEBA's AChE action that can be brought about by the bioactive components' antioxidant properties, which include phenolics, alkaloids, flavonoids, carotenoids, polysaccharides, and anthocyanins, among others (Rastogi et al., (1998; Ehassaneen et al., 2023-b; Boraey, 2023). Due to their several biological functions, including scavenging, antioxidant, and suppression of the oxidation of lipids, these bioactive chemicals protect neurons from oxidative stress harm. Conversely, serotonin and dopamine are neurotransmitters which work as chemical transmitters and assist in controlling a variety of physiological processes, involving motion, balance, emotions, sensations of reward and happiness, and metabolism and digestion (Veot and Veot, 1990). Differential neurological system disorders, including those that are worsened by obesity, have been linked to malfunction of the serotonin and dopamine systems (Nam et al., 2018). In light of this, a number of investigations have shown that the neurotransmitters serotonin and dopamine have a role in controlling appetite and body weight (Lam et al., 2010). Additionally, Nam et al. (2018) evaluated the connections between obesity and extra-striatal serotonin and striatal dopamine transporter availability. Additionally, Morton et al. (2014) showed that the brain is essential for regulating and inhibiting the prepotent reaction to food. Prior investigation has shown that many bioactive ingredients, including those in the EEBA, have the ability to improve neurological conditions. Neurological disorders

are treated based on the ability of bioactive components, such as antioxidants, to sustain healthy brain functions. Experiments have demonstrated the neuro-stimulating features of specific bioactive components, meaning that they seem to assist stimulate neurotransmitance processes via stimulating catecholamine transmitters, like serotonin and dopamine (Mousseau and Baker, 2012; Hugo et al., 2016; Boraey, 2023). In this setting, number of enzymes, most notably monoamine oxidase (MAO), break down dopamine enzymatically to produce its inactive metabolites (Lopez-Perez et al., 2015). In neurodegenerative illnesses, the suppression of MAO that may be formed by obesity and its sequale has been proposed as an additive therapy.

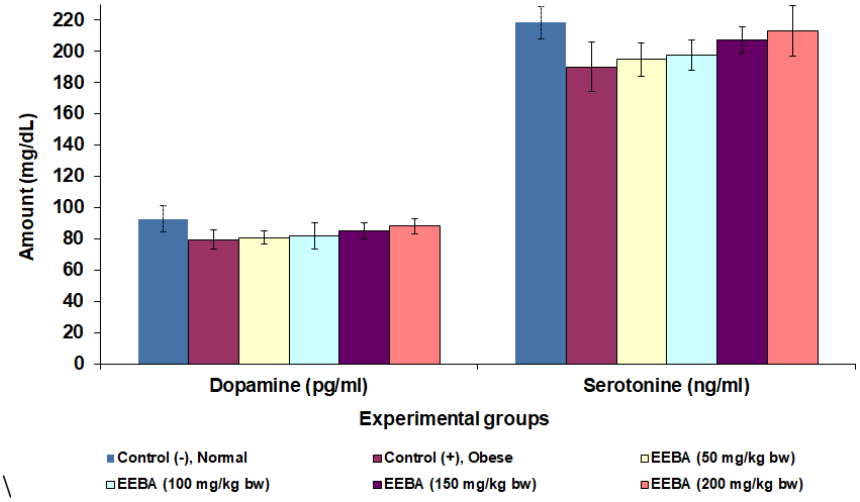

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Figure 11. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on serum dopamine and serotonin of obese rats

Every value represents mean of six rats. At P≤0.05, significant differences are explained by means in the same column with distinct superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

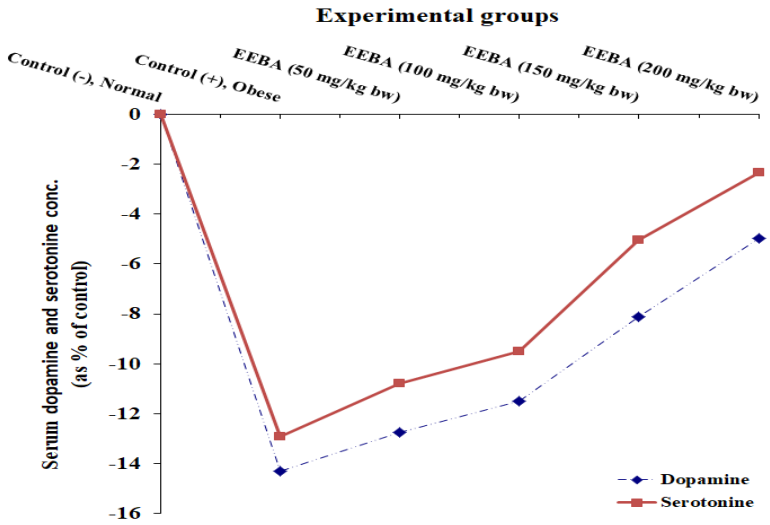

Figure 12. Impact of a dietary intervention with ethanol extract of brown algae (EEBA) on serum dopamine and serotonin (as % of control) of obese rats

Every value represents mean of six rats. At P≤0.05, significant differences are explained by means in the same column with distinct superscript letters. Control (-), normal/healthy rats without intervention; Control (+), diet induced obesity (DIO) rats without intervention; EEBA intervention, DIO rats with EEBA intervention.

Histopathological studies

Adipose tissue

Photos (1-6) illustrate the impact of ethanol extract of brown algae (EEBA) intervention on the histological analysis of the adipose tissue in obese rats. Microscopic analysis of the adipose tissue of rats in group 1 demonstrated polygonal-shaped, normal unilocular adipocytes with a signet ring appearance (Photo 1). Adipose tissue from rats in group 2 had histopathological alterations in the negative direction, including vascular congestion (Photo 2). Rats from group 3's adipose tissue, meantime, showed a modest number of small and big size unilocular adipocytes (Photo 3), along with a little infiltration of inflammatory cells (Photo 4). Examined portions of group 4 also showed a small number of large-sized unilocular adipocytes. Rats from group 5's adipose tissue showed some small-sized adipocytes (Photo 5). However, a few big size unilocular adipocytes and few small adipocytes were observed in some of the investigated sections from group 6 (Photo 6).

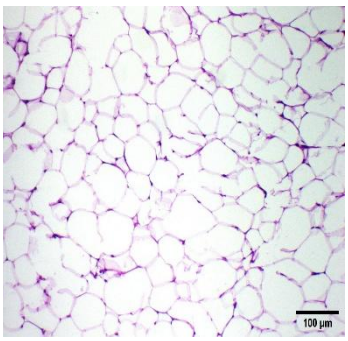

Photo 1. Rats from group 1's adipose tissue were photographed under a microscope, revealing polygonal, normally unilocular adipocytes with a signet ring appearance.

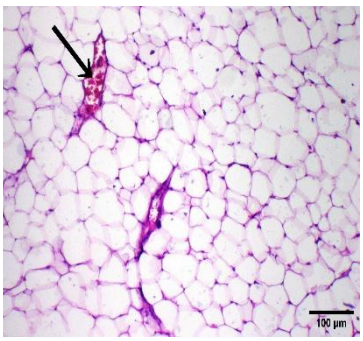

Photo 2: A photomicrograph of a rat's adipose tissue from group 2 demonstrates blood vessel congestion (arrow).

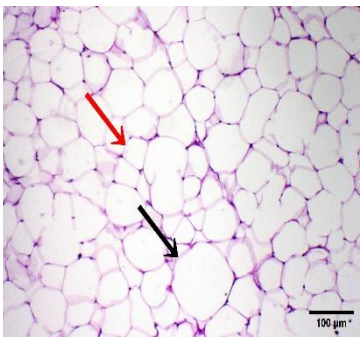

Photo 3: A photomicrograph of group 3 rats' adipose tissue reveals a limited number of small-sized adipocytes (red arrow) and a few large-sized unilocular adipocytes (black arrow).

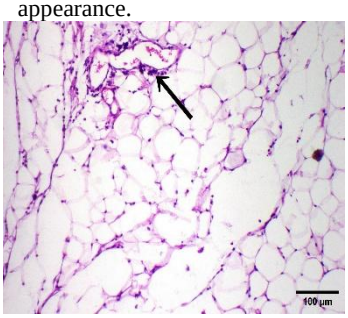

Photo 4. A photomicrograph of group 3 rats' adipose tissue demonstrates a little infiltration of inflammatory cells (black arrow).

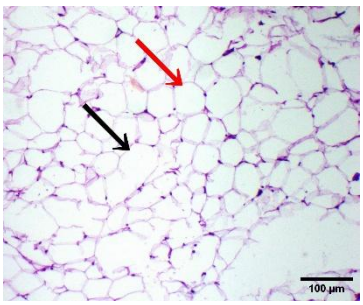

Photo 5. A photomicrograph of group 4 rats' adipose tissue reveals a reduced number of small-sized adipocytes (red arrow) and a few large-sized unilocular adipocytes (black arrow).

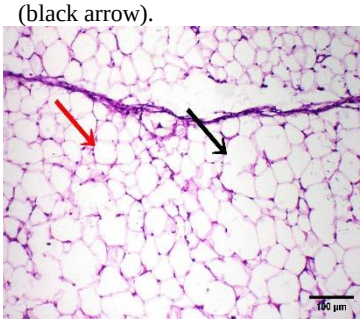

Photo 6. A photomicrograph of group 5 rats' adipose tissue reveals a reduced number of small-sized adipocytes (red arrow) and a few large-sized unilocular adipocytes (black arrow).

Figure 1. Effect of intervention with ethanol extract of brown algae (EEBA) on adipose tissue histopathological examination of obese rats (H & E, scale bar 100 µm, X 100).

Brain tissue

Figure 2 illustrates the impact of ethanol extract of brown algae (EEBA) dietary intervention on the histological analysis of the brain tissue in obese rats. The rats in group 1's cerebral cortex had no histological changes (Photo 1). Sections from group 2 showed cellular edema, necrosis, and shrunken cells (Photo 2). Sections from group 3 showed neuropil vacuolation and some neurons showing necrosis (Photo 3). Additionally, the cerebral cortex of group 4 rats showed vacuolation of the neuropil and necrosis of some neurons (Photo 4). However, the cerebral cortex of the rats in group 5 exhibited a noticeable recovery; portions that were analyzed indicated

sporadic neuron necrosis (Photo 5). At last, the rat's cerebral cortex from group 6 (Photo 6) displays no histopathological changes (H & E X 400, scale bar 50 µm).

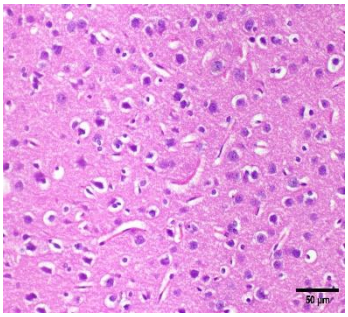

Photo 1. Cerebral cortex of rat from group 1 revealing no histological changes.

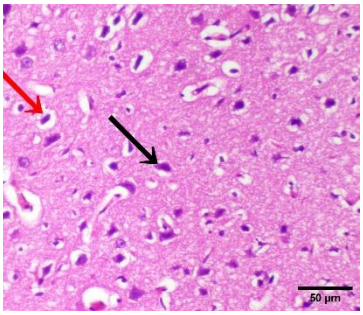

Photo 2. Cerebral cortex of rat from group 2 revealing shrunken, pyknosis of neurons and necrosis (black arrow) in addition to cellular edema (red arrow).

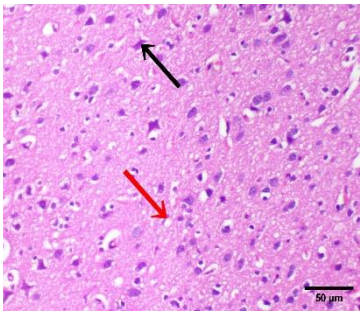

Photo 3. Cerebral cortex of rat from group 3 showing necrosis of some neurons (black arrow) and neuropil vacuolation (red arrow)

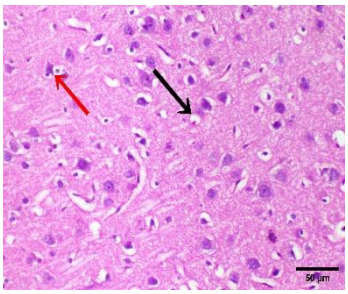

Photo 4. Cerebral cortex of rat from group 4 showing necrosis of some neurons (black arrow) and neuropil vacuolation (red arrow)

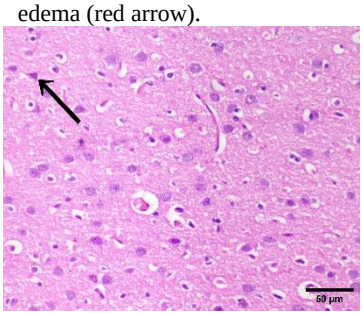

Photo 5. Cerebral cortex of rat from group 5 revealing necrosis of sporadic neurons (arrow)

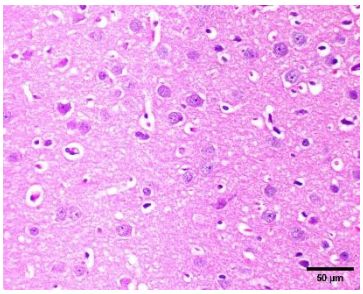

Photo 6. Cerebral cortex of rat from group 1 revealing no histopathological alterations

Figure 2. Effect of feeding intervention with ethanol extract of brown algae (EEBA) on brain tissue histopathological examination of obese rats (H & E, scale bar 100 µm, X 100)

These observations generally agree with the findings of Pannacciulli et al. (2006) and Pistell et al. (2010), who discovered that obesity was linked to reduced focal gray matter volume, changed brain function and structure, and defects in memory, executive function, and learning. Additionally, Elhassaneen et al. (2023-c) demonstrated that treatment with Silybum marianum extract, which has the same bioactive chemicals as brown algae extracts, inhibited both the development of adipocytes and the storage of fat in major fat white adipose tissues. Moreover, a high-fat diet has been associated to heart hypertrophy, fibrosis, and failure (Gabbia et al., 2022). In experimental models of NAFLD, a nutraceutical formulation including brown algae decreases hepatic lipid deposits by modifying lipid metabolism and

inflammatory processes, which impacts the activities of the adipose tissue and heart. Ultimately, the results of this research and others supported the observation that the administration of brown algae extracts to obese rats caused a satisfactory recovery of the brain muscles and adipose tissues.

Conclusion

Our theory that ethanol extract of brown algae (Sargassum subrepandum) (EEBA) .reduces obesity and its consequences in rats was validated by the study's data These complications involve positive manipulation of the obesity-linked histopathological alterations in the brain and adipose tissues of the obese rats, a reduction in the BWG, FI, and FER, an enhancement in the serum lipid profile variables, and an amelioration of neurological conditions (dopamine and serotonin content and acetylcholine esterase action). Every impact that EEBA had in obese rats was shown to be dose-dependent. These results establish a foundation for the application of EEBA in the management and prevention of obesity. Furthermore, the findings enhance the advantages of dietary modification and EEBA intervention in reducing obesity-related complications, such as neurological and histopathological problems.

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Conflict of Interests

None.

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