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Research Article

EFFECTS OF AMBERGRIS ON APPETITE AND SERUM ENDOCRINE HORMONAL LEVELS IN SKINNY SUFFERERS

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ABSTRACT

The current study evaluated the effects of ambergris on some endocrine hormones, serum lipids, body weights and appetite. A total forty subjects were recruited to receive randomly 415 mg /day of either ambergris (Am; n=20) or placebo (PL; = 20) for 4 weeks. Blood samples were used for the assessments of serum lipids, testosterone, estradiol, growth hormone (GH), prolactin, insulin, thyroxin (T_4), and cortisol. Data show significant increase in testosterone, estradiol, prolactin, insulin, cortisol, thyroxin (T_4) levels and body weights after ambergris dosing only while growth hormone showed non-significant changes in both groups. A significant increase in total cholesterol (T_c), low density lipoprotein cholesterol (LDL_c) and high density lipoprotein cholesterol (HDL_c) while significant decrease in triglycerides (TG_s) levels in ambergris group were observed. We conclude that ambergris ingestion resulted in; increase of both sexual desire and body weights due to its effect on some endocrine hormones.

Keywords: Ambergris, Insulin, Prolactin, Testosterone, Appetite

INTRODUCTION

Many factors in our food, beverages or ingestible of folklore use; affecting body metabolic controllers leading to changes our appetite and body weights. Ambergris (amber or anber) is an internal pathological secretion of only 1% of all Sperm blue Whales (*Physeter macrocephalus* L. = *P. catodon*) due seemingly to the irritation of the stomach by the beaks of octopus and certain shellfish. It is commercially available from certain companies e.g. Cadima Pathé (France); La Via del Profumo (Italy), Bernard Perrin Courtage (France); Ambergris.co.nz (New Zealand) [1, 2, 3]. The animal releases amber spontaneously to found floating on the sea, cast on the seacoast of warm countries, or it is collected from intestine of the whale after its death [4]. However, it is a fragrant substance of dark brown to black but, on exposure to sunlight, air and sea water, it gradually fades to a light gray and other chemical processes break ambrein down into a mixture of derivative products [3, 5, 6].

Since there are many constituents have been isolated from ambergris including up to 46 % of cholestanol type steroids. The major constituent of ambergris the triterpenoid ambrein (1-ambra-8, 13, 18 triene; $C_{30}H_{52}O$; 25-45 w/w); a conversion product of cholesterol and is the major component, have musk-like odour so it is used as perfume and its chemical structure was confirmed by NMR. In addition, ambrein derivatives include; epicoprostanol (3–a–hydroxy-5-b-cholestanol; a sterol; 30-40% w/w), coprostanone, chlolestanone, cholesterol, epicholestanol porphyrine, copper and fatty acids [4-10].

Moreover, many reports are available on the folklore importance of crude ambergris, on account of some excellent medicinal properties it possesses. It has been prized, not only for its use in perfumery, but also for its alleged restorative and aphrodisiac properties [3, 5, 6]. It has been used by Ancient Egyptians for scenting cigarettes [6, 11] and in Asia, besides being used as a drug, it also employed as a spice for food and wines [12]. In the eastern discipline of medicine, ambergris containing compounds and pastes were thought to be excellent curative for some nervous disorders, as well as replenish and aphrodisiac [5, 9]. A primary screening profile regarding the cholinergic and/or adrenergic effects of some fractions of ambergris has been reported earlier [13], and a few reports regarding the effects of ambrein on the cardiovascular system [14], blood glucose level [15], edema [16] and mode of action in antinociception [17] have been published from the same laboratory. Similarly, Epicoprostanol has been evaluated from the same laboratory for some hormonal levels, anti-inflammatory and antipyretic activity, changes in plasma biochemistry, protection against experimental models of insulitis and smooth muscle responses have already been published [10, 18-23].

In Yemen and other Arabic countries, ambergris has been used in folk medicine for gaining weight and as aphrodisiac. Its effect on weight gaining may continue for several years after use of ambergris especially if its users were at younger age or at age before puberty. These folklore uses of ambergris attract many skinny individuals to use it particularly here in Yemen. Therefore, the purpose of present study is to evaluate the ambergris effects at its folklore dose on levels of some endocrine hormones [testosterone, estradiol, GH, prolactin, insulin, cortisol, and thyroxin (T_4)], levels of serum lipids, changes in menstruation, appetite, and body weight in Yemeni skinny subjects.

MATERIALS AND METHODS

Equipments

Electric balance (Sartorius AG- Göttingen Germany BP310S), Centrifuge (Hernie Z 400, Wehingen), ELIZA reader (Humareader Human Company 2106/1682), UV/Visible Spectrophotometer (Shimadzu), refrigerator, deep freeze, micropipette of different size, and plastic syringe were used.

Ambergris source, description and dose

Source and description of ambergris

Ambergris samples were purchased from AL-Nasheri, local market in Sana'a of Yemen Republic (They import it from Nisha International Pte Ltd, *Singapore*). Description of ambergris: Samples of ambergris were blackish to pale gray type, which is called Dokhni ambergris as a traditional name. Ambergris gets its name from the French "ambre gris" (gray amber) to distinguish it from the fossilized resin, brown amber. Ambergris described according to Nisha International Pte Ltd, as raw material of ambergris results from a pathological condition of the sperm whale *Physeter macrocephalus* L. syn *P. catodon* L. In the normal course of events, calculus (sand and stones) or cachalot is regularly ejected from the digestive tracts from adult sperm whales. Fresh material is almost black turning to light gray as it matures. It contains 46% of cholestanol type sterols including (+)-epi-coprosterine and the triterpene alcohol (-)-ambreine (25-45%), which is odorless, but this material is the precursor to other fragrant compounds formed by auto-oxidation, sunlight, and seawater such as (-)-gamma-cyclogeranyl chloride and (-)-gamma-bicyclohomofarnesal. The identity of this material was verified by the Research Center of College of Pharmacy, Sana'a University, Sana'a of Yemen and a voucher specimen was kept on record (RC-23112010).

Ambergris dose

A folklore dose of ambergris is approximately 11.6 grams/1 Kg of honey bees or / 1500 mL of milk and taken as one teaspoonful after 12 hour of overnight fasting for 4 weeks. In the present study we depend on the above folklore dose except using skim instead honey bees or milk. The samples were grounded and weighed to give 415 mg in each single dose, which added freshly and daily to 50 ml of skimmed milk, coded and preserved in the refrigerator not for more than 12 hours before use.

Participants and protocol design

Inclusion criteria

In the present study a randomized double-blind placebo-controlled trial design was used. Forty participants of average ages (21±1.3), their gender was 20 male and 20 female. They were skinny and want to gain weight. A written informed consent was obtained from all participants in the study. The study followed guidelines of the Declaration of Helsinki and Tokyo for humans. The study had Medicine and Health Sciences College of Sana'a University Ethics and Human Experimentation Committee approval.

Exclusion criteria

Subjects suffering from any acute, chronic, or parasitic diseases and those with anorexia nervosa were excluded from the present study. In addition, smokers, lactating- or pregnant-women, on steroid-, insulin-, thyroxin-, bromocriptine-, or tamoxifen-therapy were excluded from the present study.

Protocol design

Participants were assigned randomly to either therapeutic (Ambergris; Am) or sub-therapeutic (placebo; PL) using a numbered series of opaque sealed envelopes prepared in advance of the trial. Participants in two groups were receiving 415 mg of either ambergris (Am) or starch (PL) in 50 mL of skimmed milk/day after 12 hours of overnight fasting for 4 weeks. Participants instructions: All subjects were instructed by the research nutritionist and medical supervisor to keep a written record of their food intakes (3 days including one weekend day), body weight (weekly), number of sexual desire (weekly) and menstrual changes (at end of the month).

Blood sample withdrawal

All blood samples were collected after 12 hour of overnight fasting, between 8:00 a.m. and 10:00 a.m. to minimize the effect of either food or daily fluctuation. Technician staffs at biochemistry research laboratory of medicine and health sciences collage of Sana'a University were blind to both research protocol and coded samples. Blood samples were collected before randomization to obtain base line data and at 2 hour after last dose of ambergris or placebo at end of 4 weeks. Serum was separated, preserved at –20 ^{0}C for measurements of growth hormone (GH), prolactin, insulin, thyroxin (T_4), cortisol, testosterone (males), and estradiol (females) by ELISA method (within 2 days of collection). In addition, serum levels of triglycerides (TGs), total cholesterol (Tc), low density lipoprotein cholesterol (LDL_C), and high density lipoprotein cholesterol (HDL_C) were measured by colorimetric methods (within one week).

Biochemical estimation/assay

All hormones were measured by ELISA, growth hormone was measured as described by Colao et al. [24], testosterone was measured as described by Tietz [25], estradiol was measured as described by Racliff et al. [26], cortisol was measured as described by Crapo [27], thyroxin (T_4) was measured as described by Schuurs, and Van Weeman [28], insulin was measured as described by Frier et al. [29] and prolactin was measured as described by Uotila et al. [30] (DRG International, Inc., USA). Serum lipids were measured by colorimetric methods; TGs were estimated using the phosphate oxidase method as described by Trinder [31], total cholesterol was estimated using the Chod – pap method as described by Zoppi and Fellini [32], LDL_C was measured as described by Kerscher et al. [33], HDL_C was estimated using the dextran – sulphate Mg (II) method as described by Wieland and Siedel [34].

Statistical analysis

All results were expressed as mean ± S. E. M. Results were analyzed using student-t-test to compare data at baseline with those at end point of treatment within each group, while p-value < 0.05 was considered statistically significant (using SPSS statistics software program, version 15).

RESULTS

Data show significant increase in both sex hormones either in males or females (testosterone and estradiol respectively; $P < 0.001$ and $P < 0.01$ respectively) after ambergris dosing, while non-significant change in placebo group. In addition, the measured pituitary hormones (GH and prolactin) showed slightly different pattern, GH show non-significant difference in both groups after dosing either ambergris or placebo, while significant increase ($P < 0.01$) in prolactin after ambergris dosing only. Moreover, insulin, cortisol and T_4 showed significant increase ($P < 0.001$, $P < 0.01$, and $P < 0.01$ respectively) after ambergris dosing, while non-significant change in placebo group [data shown in **Tables 1** and **Fig 1**].

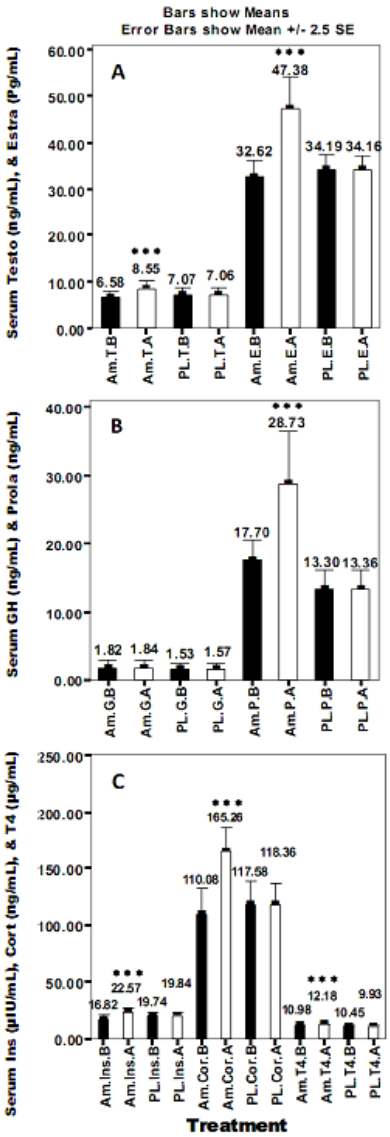

Fig 1: Effects of ambergris (Am) or placebo (PL) dosing (415 mg/day for 4 weeks) on testosterone, estradiol [A], growth hormone, prolactin [B], cortisol, thyroxine and insulin [C] serum levels in its users (* *P < 0.001* vs. baseline data). T or Testo = testosterone; E or Estra = estradiol; G or GH= growth hormone; P or Prola = prolactin; Cor or Cort = cortisol; T4 = thyroxine; Ins = insulin; B = before; and A = after.**

Table 1: Effects of Ambergris or Placebo Oral Dosing on Serum Levels of Testosterone, Estradiol, GH, Prolactin, Insulin, Cortisol and Thyroxin (T_4) Hormones in its Users

Treatments	Testosterone (ng/mL) n=10 (male)		Estradiol (Pg/mL) n=10 (Females)		GH (ng/mL) n=20		Prolactin (ng /mL) n=20		Insulin (µIU/mL) n=20		Cortisol (ng/mL) n=20		T_4 (µg/dL) n=20	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Placebo (415 mg starch/ day for 4 weeks)	7.07±0.65	7.06±0.66	34.19±1.28	34.16±1.22	1.53±0.34	1.57±0.34	13.3±1.12	13.36±1.09	19.73±1.11	19.84±1.04	117.58±8.37	118.37±7.6	10.45±0.27	9.93±0.58
Ambergris (415 mg ambergris /day for 4 weeks)	6.58±0.54	8.55±0.65***	32.62±1.45	47.38±2.72***	1.82±0.44	1.83±0.43	17.7±1.16	28.7±3.1***	16.82±1.46	22.57±1.68***	110.07±9.08	165.27±8.39***	10.98±0.21	12.17±0.22***

n = number of subjects (mean ± S.E.M); GH = Growth Hormone; T_4 = Thyroxin; *** = P < 0.001 vs. baseline data in each group.

In the same line, serum lipids data showed significant increase (P < 0.001) in T_c, LDL_c and HDL_c while significant decrease (P < 0.001) in TGs levels after ambergris dosing while non-significant changes in all serum lipids of placebo group [data shown in **Table 2]**.

Table 2: Effects of Ambergris or Placebo Oral Dosing on Serum Lipids in its Users

Treatments	TGs (mg/dL) n=20		Tc (mg/dL) n=20		LDL_C (mg/dL) n=20		HDL_C (mg/dL) n=20	
	Before	After	Before	After	Before	After	Before	After
Placebo (415 mg starch/day for 4 weeks)	103 ± 2.4	103.45±2.5	110.9±7.4	110.8±7.2	56.5±3.6	56.6±3.7	65.45±3.8	65.16±3.7
Ambergris (415 mg ambergris/day for 4 weeks)	106.15±2.8	98.1±3.15***	87.9±6.5	119.1.4±6.5***	35.05±3.7	53.9±3.5***	46±3.2	60.2±3.4***

n = number of subjects (mean ± S.E.M); TGs = Triglycerides; Tc = Total cholesterol; LDL_C = Low Density Lipoprotein Cholesterol; HDL_C = High Density Lipoprotein Cholesterol; *** = P < 0.001 vs. baseline data in each group.

Data of body weights showed highly significant increase (P < 0.001) at all interval points after ambergris dosing when compared with base line data of body weights while non-significant changes in body weights of placebo group at all interval points, except slightly significant increase at 3rd and 4th weeks when compared with base line data of body weights [data shown in **Fig 2]**.

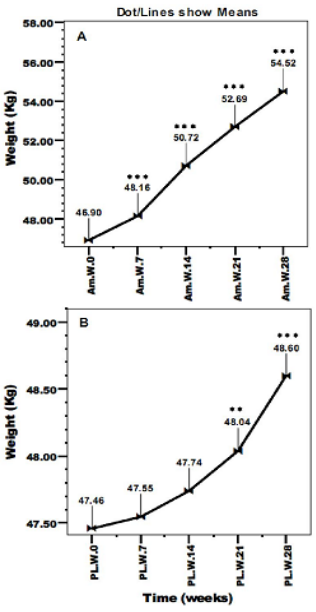

Fig 2: Effects of ambergris (Am) [A] or placebo (PL) [B] dosing (415 mg/day for 4 weeks) on body weights means in its users (*P < 0.01,* *** *P < 0.001* **vs. baseline data). W = week.**

Table 3 showed significant increase in percentage of sexual desire and appetite after ambergris dosing than placebo. Moreover, significant changes in menstruation (amenorrhea) after ambergris dosing while none changes with placebo.

Table 3: Effects of ambergris or placebo oral dosing on sexual desire, menstruation and appetite in its users

Treatments	Changes					
	Sexual desire n = 20		Menstrual disturbance n = 10		Appetite n = 20	
	Number	%	Number	%	Number	%
Placebo (415 mg starch/day for 4 weeks)	No change	0 %	No Change	0 %	Increased in 2 individuals	10 %
Ambergris (415 mg ambergris/day for 4 weeks)	Increased in 13 individuals	65 %	Observed as amenorrhea in 6 individuals	60 %	Increased in 18 individuals	90 %

DISCUSSION

In Arabian society ambergris was named 'anbar' and from this word the European name ambergris was derived. They used ambergris to treat heart and brain diseases, headaches, rheumatism, constipation, common colds, and as aphrodisiac [10, 35, 36]. However, the biochemistry of ambergris in the scientific literature is still largely on a speculative level and there is no published data about ambergris effects on most of human endocrine hormones.

The results of the current study show increase of serum testosterone levels in male subjects after ambergris ingestion. These results are in agreement with study of Taha and Islam [19] whom states that ambrein (as major constituent of ambergris) treatment was found to elevate plasma testosterone levels. In addition, the present results were in the same line with Taha & his college [37] whom reported that administered 100 and 300 mg of ambrein/kg rat bodyweight, increased sexual behavior in male rats via increased their number of

penile erections in the absence of females, as well as increased intromissions and anogenital investigatory behavior in the presence of females.

Since, there are many other constituents have been isolated from ambergris, including ambrein non-volatile derivatives; epicoprostanol, coprostanone, chlolestanone, cholesterol, epicholestanol porphyrine, copper and fatty acids [7, 8]. The elevation of both testosterone and estradiol levels with ambergris ingestion could not be explained by effect of ambrein only but also by effect of non-volatile derivatives of it, which could be act as a precursor for the synthesis of steroid hormones including testosterone, estradiol, and cortisol hormones. This explanation depends on a similarity in chemical structure (the structure of ambrein betrays its cholesterol origin and structural similarity to steroid nucleus) and stay just theoretical explanation and needs further future research.

Increased total thyroxin (T_4) serum levels with ambergris ingestion might be due to previously increased glucocorticoids which stimulate protein breakdown in peripheral tissues, exposing tyrosine to being involved in thyroid hormone synthesis [38] or due to estrogen-induced increase in the serum concentration of thyroxin-binding globulin [39].

Here, the decreased serum levels of TGs after ambergris ingestion could be explained by formerly increased levels of cortisol, insulin and thyroxin. Insulin and thyroxin activate lipoprotein lipase in blood leading to the clearance of plasma from triglycerides while cortisol induces lipolysis particularly in peripheral tissue leading to decrease levels of TGs and increased levels of free fatty acids. The increased free fatty acids lead to insulin resistance as reported by Boden [40]. Thereby the resulted increase in insulin level as reported here after ambergris ingestion, might be due to the decreased sensitivity of insulin receptors by elevated cortisol and thyroxin levels. Studies in man have found that glucocorticoids can decrease insulin receptor binding affinity without decreasing insulin receptor numbers [41], decrease receptor number and affinity [42, 43]. On the other hand, central actions of glucocorticoids may enhance vagal stimulation of insulin secretion [44].

These results and its explanation, in contrast to the results reported by Taha [15], which states that ambrein reduce the blood glucose levels of normal and moderately alloxan-diabetic rats but did not reduce the blood glucose levels of severely-diabetic rats. This difference might be due to using ambrein alone (not a crude ambergris) in treating induced diabetes in rats.

As mentioned before, the structure of ambrein betrays its cholesterol origin. However, increased levels of total and individuals of cholesterol could attributed to that free fatty acid liberated from lipolysis; favorably oxidized in the presence of higher level of total T_4 into acetyl-CoA, which acts as building units for cholesterol synthesis. In addition, ambergris containing ambrein derivatives act as precursors of cholesterol synthesis [5, 6].

In the results of the present study, ambergris ingestion shows significant increase in body weight of its users. However, many reports and information from unpublished data mentioned that ambergris used as an appetizer, to increase body weight in both male and female. It was used usually with honey bees. In Arabic folk medicine, it is used to increase appetite, sexual ability, and body weight and these reports in the same line with the results of the present study. Increased weights of subjects as an effect of ambergris ingestion, may be due to the effects of elevated anabolic hormones including; insulin, testosterone, and estradiol which acts to increase protein synthesis and water retention respectively. This hypothesis in some, in agreement with Tietz [45] who reported that androgens and growth hormones increases protein synthesis and serum protein levels. The non-significant increase in GH level in serum of subjects, might due to a response to the increased levels of cortisol, steroid hormones and increased glucose level according to hypothesize insulin resistance.

These data supported by recorded changes in appetite, sexual desire and menstrual changes after ambergris use. As a result of increased levels of testosterone, estradiol, and prolactin with ambergris ingestion; sexual desire increased and menstrual cycle disturbed or ceased respectively. Since increased level of prolactin stimulate corpus luteum to secrete progesterone and inhibits ovulation.

In addition, possibly increased levels of insulin and thyroxin result in improvement of appetite. In contrast, glucocorticoids oppose other actions of insulin, including its effect to reduce central appetite [46]. Moreover, sex hormones, i.e. estrogen, progesterone, and androgens, play an important role in the regulation of appetite and energy metabolism [47]. Testosterone is known to stimulate appetite [47]. In contrast to estrogen, progesterone seems to stimulate appetite. Several studies in women have demonstrated a distinct increase in food intake in the premenstrual period of the menstrual cycle, when progesterone levels are high [48, 49, 50].

We conclude that ambergris ingestion at its folklore dose resulted in an increase of both sexual desire and body weights due to its effect on some endocrine hormones. Thereby the ambergris-modified testosterone levels support the folk use of this drug as aphrodisiac or sexual stimulant. Moreover, ambergris increases body weight in the region of protein synthesis without obesity, due to the effects of increased anabolic hormones and increased lipolysis. We recommend for further intensive research; to determine ambergris effects on other endocrine hormones such as progesterone and blood glucose; to raise awareness in the minds of its users where amber considered as hormonal therapy. The ambergris might be used as nutritional therapy (as an anabolic agent) for patients with anorexia nervosa. However, the present study showed that ambergris increases prolactin, cortisol and thyroxin, thereby ambergris avoided to prescribe for infertile female, diabetic and hyperthyroidism suffering patients.

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Conflict of interest: The authors declare that there are none conflict of interest.

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