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Attorneys for Defendant
Iovate Health Sciences U.S.A. Inc.

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

MOHAMMED DABOUSSI, on behalf of himself, all others similarly situated, and the general public,

Plaintiff,

vs.

IOVATE HEALTH SCIENCES U.S.A., INC. and DOES 1 -10,

Defendants.

Civil Action No. 2:16-cv-8049

Los Angeles County Superior Court No. BC635205

DEFENDANT IOVATE HEALTH SCIENCES U.S.A. INC.'S NOTICE OF REMOVAL OF ACTION UNDER 28 U.S.C. §§ 1332(a), 1441 [DIVERSITY], AND §§ 1332(d), 1453 [CAFA]

PLEASE TAKE NOTICE THAT Defendant Iovate Health Sciences U.S.A. Inc. ("Iovate") hereby removes this action from the Superior Court of the State of California, County of Los Angeles, to the United States District Court for the Central District of California, Western Division, pursuant to 28 U.S.C. §§ 1332(a), 1332(d), 1441, 1446, and 1453. As grounds for removal, Iovate states as follows:

PRELIMINARY STATEMENT

1. This Action is a civil action of which this Court has original jurisdiction under the Class Action Fairness Act of 2005 ("CAFA"), 28 U.S.C. § 1332(d), and 28 U.S.C. § 1453, on the grounds that: (a) this action is a proposed "class action" as defined in 28 U.S.C. § 1332(d)(1)(B); (b) Defendant is a Delaware corporation with its principal place of business in Ontario, Canada; (c) no other defendant is a citizen of California; (d) Plaintiff is a resident of California who seeks to represent a putative class of California consumers; and (e) the amount in controversy based on the allegations placed at issue in the Complaint exceeds $5,000,000.

2. Iovate generally denies the allegations made by plaintiff Mohammed Daboussi ("Plaintiff"), disputes the claims asserted by Plaintiff, and disputes that Plaintiff is entitled to any relief. Iovate discusses Plaintiff's allegations and claims solely to demonstrate the proprietary of removal.

NATURE OF THE ACTION

3. This action was commenced on September 26, 2016, with the filing of a complaint ("Complaint") in the Superior Court of the State of California, County of Los Angeles, styled *Mohammed Daboussi v. Iovate Health Sciences, U.S.A., Inc.*, case number BC635205.

4. The Complaint alleges a variety of claims against Iovate arising out of the sale of Garcinia Cambogia Plus, Garcinia Cambogia Plus Gummies, Coconut Oil, Green Coffee Bean, Matcha Green Tea Plus, Probiotics Plus Weight Loss, Raspberry Ketones Plus, Konjac Root Plus, Xendadrine Core, and Xemdadrine Ultimate (the "Weight Loss Products"). These claims include alleged violations of California's

Unfair Competition Law, Cal. Bus. & Prof. Code § 17200 *et seq*, California's False Advertising Law, Cal. Bus. & Prof. Code § 17500 *et seq*, California's Consumer Legal Remedies Act, Cal. Civ. Code § 1750 *et seq*, breach of express warranties, Cal. Comm. Code §2313(1), and breach of implied warranty of merchantability, Cal. Comm. Code § 2314.

5. Plaintiff seeks relief on behalf of a putative class of purchasers of Iovate's produces defined as "all persons in California who in the past four years (the "Class Period"), purchased, for personal or household use, and not for resale or distribution purposes, any of the Weight Loss Products." (Compl. ¶ 34.)

6. The Complaint seeks money damages, restitution, disgorgement of all monies, revenues, and profits obtained by means of any wrongful or unlawful act or practice, injunctive relief, and other relief including reasonable attorneys' fees, costs, expenses, pre-judgment interest, and post-judgment interest.

7. Iovate is the only defendant named in the Complaint. Iovate is not aware of the existence of, or service of any "Doe" defendant; consequently no further consent to removal is required.

8. This notice of removal is timely under 28 U.S.C. § 1446 because service of the Summons and Complaint has yet to occur to date.

REMOVAL IS PROPER BECAUSE THIS COURT HAS ORIGINAL JURISDICTION PURSUANT TO 28 U.S.C. §§ 1332, 1441, and 1453

9. As set forth more fully below, removal is proper under 28 U.S.C. §§1332(d) and 1453 because this case is (a) proposed "class action" as defined in 28 U.S.C. 1332(d)(1)(B); (b) in which the Plaintiff and the putative class members are citizens of a state different from Iovate; and (c) the amount in controversy exceeds $5,000,000. Alternatively, removal is proper pursuant to 28 U.S.C. §1332(a) and 1441(a) because there (a) there is complete diversity of citizenship and (b) the amount in controversy exceeds $75,000.

Removal Pursuant to 28 U.S.C. §§ 1332(d) and 1453

10. This Court has original subject matter jurisdiction over this action pursuant to CAFA. *See* 28 U.S.C. § 1332(d). Pursuant to CAFA, a federal district court shall have original jurisdiction of any "class action" composed of 100 or more putative class members, where any member of the proposed class is a citizen of a state different from any defendant, and the amount placed in controversy exceeds $5,000,000 (exclusive of interest and costs). *See* 28 U.S.C. § 1332(d). Moreover, CAFA "abrogates the rule against aggregating claims" to reach the threshold amount in controversy requirement. *Exxon Mobil Corp. v. Allapattah Servs., Inc.*, 545 U.S. 546, 571 (2005); *see also* 14A Charles Alan Wright & Arthur R. Miller, Federal Practice & Procedure § 3704 (3d ed. 2010) ("[CAFA] ... provides for aggregation even if no individual class member asserts a claim that exceeds $75,000.").

11. In the Ninth Circuit, when the complaint does not contain any specific amount of damages sought, the party seeking removal under diversity bears the burden of showing by preponderance of the evidence that the amount in controversy exceeds the statutory amount. *Lewis v. Verizon Communications Inc.*, 627 F.3d 395, 397 (9th Cir. 2010) (citing *Guglielmino v. McKee Foods Corp.*, 506 F.3d 696, 699 (9th Cir. 2007)); *Lowdermilk v. United States Bank Natl Ass'n*, 479 F.3d 994, 1000 (9th Cir. 2007).

12. Although the Complaint does not allege a damages or restitution amount as to the claims, removal is proper if, from the allegations of the Complaint and the Notice of Removal, it is more likely than not that the amount in controversy exceeds $5 million. *See Lowdermilk v. United States Bank Nat'l Ass'n*, 479 F.3d 994, 1000 (9th Cir. 2007). The aggregated claims in the Complaint more likely than not satisfy CAFA's $5 million amount in controversy requirement.

13. In the Complaint, Plaintiff seeks, *inter alia*, injunctive relief and an order requiring Defendants to conduct a corrective advertising campaign, disgorge or return "all monies, revenues, and profits obtained by means of any wrongful act or practice," restitution to restore all funds acquired by means of any act or practice declared by the

Court to be unlawful, unfair or fraudulent." (Compl. at 22:3-4, 22:5-7.) Although Iovate denies the validity of Plaintiff's individual and class action claims, the class stands to recover in excess of $5 million based on the allegations set forth in the Complaint.

14. Moreover, if the class action is successful, the class would be entitled to recover attorneys' fees, which are sought in the Complaint. (Compl. ¶ 22:9-10.) Courts have held that an award of attorneys' fees, if such fees are specifically authorized by statute, may be considered for purposes of calculating the amount in controversy. *See Brady v. Mercedes-Benz USA, Inc.* 243 F. Supp. 2d 1001, 1004 (N.D. Cal 2002) ("Where the law entitles the prevailing plaintiff to recover reasonable attorney's fees, a reasonable estimate of fees likely to be incurred to resolution is part of the benefit permissibly sought by the plaintiff and thus contributes to the amount in controversy."). Here, if Plaintiff and/or the putative class succeed on the CLRA claim, recovery of attorneys' fees is statutorily authorized. *See* Cal. Civ. Code § 1780(e).

15. Furthermore, Plaintiff and the purported class seek injunctive relief. (Compl. at 21:24-27; 22:1-2.) Costs of compliance with an injunction are relevant in ascertaining whether the amount in controversy is satisfied. *See Guglielmino v. McKee Food Corp.*, 506 F.3d 696, 701 (9th Cir. 2007) (removal is proper under CAFA where defendants make a showing that the aggregate costs of complying with the requested injunctive relief will likely exceed $5,000,000). Moreover, according to the Report of the Senate Judiciary Committee on the Act:

> "[I]n assessing the jurisdictional amount in declaratory relief cases, the federal court should include in its assessment the value of all relief and benefits that would logically flow from the granting of the declaratory relief sought by claimants. For example, a declaration that a defendant's conduct is unlawful or fraudulent will carry certain consequences, such as the need to cease and desist from that conduct, that will often 'cost' the defendant in excess of $5,000,000."

S. REP. 109-14 (2005), *43, 2005 U.S.C.C.A.N. 3, **41. As such, the amount in controversy must include not only the amount of damages that the putative class would receive, but also the costs of complying with any injunctive relief ordered in this action pursuant to the class claims. Pursuant to the CLRA, Plaintiff individually and on behalf of the purported class seeks an injunction barring any practice set forth in the Complaint. (Compl. ¶ 70.) As Plaintiff challenges the label claims for Iovate's Weight Loss Products, this request effectively seeks to prevent Iovate from providing the product to retailers, *i.e.*, effectively pulling the Weight Loss Products from California stores.

(a) The costs complying with such an order make clear the amount at issue in this case exceeds $5 million, and Plaintiff does not allege otherwise in the Complaint. Indeed, according to a study released by the American Society for Quality in August 2003, each product recall costs an organization "more than $8 million on average in reimbursement to the customer, recall implementation costs, and compensatory damages. This figure does not include lost sales and lost market share." *Quality Progress*, Vol. 36, No. 8, August 2003, pp. 41-49 (available at http://asq.org/qic/display-item/index.pl?item=l9199); *see also*, ABA Section of Business Law, Business Law Today, September/October 1999 ("More recently, Casablanca Fan Co.'s recall in 1997 affected 3.3 million ceiling fans with a retail value of $700 million. Similarly, Black & Decker's recall in 1997 of 750,000 coffee makers affected retail sales of approximately $49 million.") (available at http://www.abanet.org/buslaw/blt/9-1recall.html).

(b) Injunctive relief would not only require a recall of all of the Weight Loss Products in California, but could require Iovate to recall products throughout the United States and abroad, for which it would incur significant costs. Iovate provides the Weight Loss Products to national chains and online retailers; it would be unable to prevent those retailers from selling in California the Weight Loss Products as currently packaged. Thus, in order to protect Iovate's interests and ensure it is not deemed to

have violated any potential injunction, Iovate would have to engage in a nationwide recall and redesign of the Weight Loss Products packaging. *Id.* Moreover, retailers have policies which preclude California specific labeling.

16. Although Iovate denies that it is liable to any individual or that class treatment is appropriate for this case, removal is proper pursuant to 28 U.S.C. § 1332(d) and 1453 because the state court action is an action between citizens of different states, on behalf of a putative class numbering thousands, and involves an amount in excess of $5,000,000.

Removal Pursuant to §§ 1332(a) and 1441

17. To determine diversity of citizenship in the context of diversity jurisdiction, a corporation is a citizen of (1) the state under whose laws it is organized or incorporated; and (2) the state of its "principal place of business." 28 U.S.C. § 1332(c)(1). A corporation's principal place of business is solely determined by the state of its "nerve center." *Hertz Corp. v. Friend*, 559 U.S. 77, 130 S. Ct. 1181 (2010). A corporation's nerve center is "where a corporation's officers direct, control, and coordinate the corporation's activities . . . [a]nd in practice it should normally be the place where the corporation maintains its headquarters—provided that the headquarters is the actual center of direction, control, and coordination." *Id.* at 1192.

18. Iovate is a citizen of Delaware because that is its state of incorporation and a citizen of Canada because that is where the company's "nerve center" is located. From before the filing of the Complaint to the present, Iovate has not been a California citizen.

19. The amount in controversy requirement is satisfied because the Complaint seeks an order requiring Defendants to conduct a corrective advertising campaign, disgorge or return all monies, revenues and profits obtained by means of any wrongful act or practice, restitution to restore all funds acquired by means of any act or practice declared by the Court to be unlawful, unfair or fraudulent, and reasonable attorneys'

fees. (Compl. at 21:24-22:10.) Accordingly, the amount in controversy is over $75,000 based on the relief sought.

ALL OTHER STATUORY REQUIREMENTS FOR REMOVAL ARE SATISFIED

1. Venue is proper in this district, pursuant to 28 U.S.C. § 1441(a), because Plaintiff filed his action in the Superior Court of California for the County of Los Angeles. The United States District Court for the Central District of California is the "district and division embracing the place where such action is pending." 28 U.S.C. § 1441(a).

2. Removal is timely because Iovate has yet to be served with process and the Complaint in the Action to date. 28 U.S.C. § 1446(b).

3. To date, there are no "process, pleadings, and orders served upon" Iovate in this Action. 28 U.S.C. § 1446(a). (Ferrell Decl. ¶ 2.) Nevertheless, attached to this Notice of Removal is a copy of the Complaint in this Action, which Iovate obtained not via proper service of process of the Summons and Complaint. (Ferrell Decl. ¶ 3 Ex. 1.)

4. Iovate will promptly serve Plaintiff with this Notice of Removal and will promptly file a copy of this Notice of Removal with the clerk of the Superior Court of the State of California for the County of Los Angeles. 28 U.S.C. § 1446(d).

5. Iovate reserves the right to amend or supplement this Notice of Removal.

6. Iovate also reserves all defenses, and the filing of this notice of removal is subject to, and without waiver of, all available defenses.

WHEREFORE, Iovate respectfully removes this action from the Superior Court of the State of California for the County of Los Angeles to this Court.

Date: October 28, 2016

PACIFIC TRIAL ATTORNEYS
A Professional Corporation

By: */s/Scott J. Ferrell*
Scott J. Ferrell
Attorneys for Defendant
Iovate Health Sciences U.S.A. Inc.

CERTIFICATE OF SERVICE

(United States District Court)

I am employed in the County of Orange, State of California. I am over the age of 18 and not a party to the within action; my business address is 4100 Newport Place Drive, Suite 800, Newport Beach, CA 92660.

On October 28, 2016, I have served the foregoing document described as **DEFENDANT IOVATE HEALTH SCIENCES U.S.A. INC.'S NOTICE OF REMOVAL OF ACTION UNDER 28 U.S.C. §§ 1332(a), 1441 [DIVERSITY], AND §§ 1332(d), 1453 [CAFA]** on the following person(s) in the manner(s) indicated below:

Martin E. Jerisat 2372 Morse Ave., Suite 322 Irvine, CA 92614 714-571-5700	
Gordon G. Phillips 1600 North Broadway, Suite 650 Santa Ana, CA 92706 714-541-3000	

[ ] (BY ELECTRONIC SERVICE) I am causing the document(s) to be served on the Filing User(s) through the Court's Electronic Filing System.

[X] (BY MAIL) I am familiar with the practice of Pacific Trial Attorneys for collection and processing of correspondence for mailing with the United States Postal Service. Correspondence so collected and processed is deposited with the United States Postal Service that same day in the ordinary course of business. On this date, a copy of said document was placed in a sealed envelope, with postage fully prepaid, addressed as set forth herein, and such envelope was placed for collection and mailing at Pacific Trial Attorneys, Newport Beach, California, following ordinary business practices.

[X] (FEDERAL) I declare that I am employed in the offices of a member of this Court at whose direction the service was made.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this Certificate is executed on October 28, 2016, at Newport Beach, California.

Mandy K. Jung

Scott J. Ferrell, Bar No. 202091
sferell@trialnewport.com
David W. Reid (Bar No. 267382)
dreid@pacifictrialattorneys.com
Richard H. Hikida (Bar No. 196149)
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PACIFIC TRIAL ATTORNEYS
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Tel: (949) 706-6464
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Attorneys for Defendant
Iovate Health Sciences U.S.A. Inc.

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

MOHAMMED DABOUSSI, on behalf of himself, all others similarly situated, and the general public,

Plaintiff,

vs.

IOVATE HEALTH SCIENCES U.S.A., INC. and DOES 1 -10,

Defendants.

Case No. 2:16-cv-8049

DECLARATION OF SCOTT J. FERRELL IN SUPPORT OF DEFENDANT IOVATE HEALTH SCIENCES U.S.A. INC.'S NOTICE OF REMOVAL OF ACTION UNDER 28 U.S.C. §§ 1332(a), 1441 [DIVERSITY], AND §§ 1332(d), 1453 [CAFA]

[Notice of Removal filed concurrently herewith]

DECLARATION OF SCOTT J. FERRELL

I, Scott J. Ferrell, hereby declare as follows:

1. I am an attorney licensed to practice law in the States of California and Texas, as well as in all of the federal judicial districts therein. I am the founding partner of Pacific Trial Attorneys, P.C., counsel for Defendant Iovate Health Sciences Inc. ("Iovate"). If called upon as a witness, I could and would competently testify to the facts set forth below, as I know each to be true based on my own personal knowledge or based upon my review of the files and records maintained by Pacific Trial Attorneys, P.C. in the regular course of business.

2. To date, I am not aware of any "process, pleadings, and orders served upon" Iovate within the meaning of 28 U.S.C. § 1446(a) in this Action.

3. Attached hereto as **Exhibit "1"** is a true and correct copy of the file-stamped Complaint in this Action, which my law firm obtained not via proper service of process of the Summons and Complaint.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. This declaration was executed on October 28, 2016.

/s/ Scott J. Ferrell
Scott J. Ferrell

CERTIFICATE OF SERVICE

(United States District Court)

I am employed in the County of Orange, State of California. I am over the age of 18 and not a party to the within action; my business address is 4100 Newport Place Drive, Suite 800, Newport Beach, CA 92660.

On October 28, 2016, I have served the foregoing document described as **DECLARATION OF SCOTT J. FERRELL IN SUPPORT OF DEFENDANT IOVATE HEALTH SCIENCES U.S.A. INC.'S NOTICE OF REMOVAL OF ACTION UNDER 28 U.S.C. §§ 1332(a), 1441 [DIVERSITY], AND §§ 1332(d), 1453 [CAFA]** on the following person(s) in the manner(s) indicated below:

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Gordon G. Phillips 1600 North Broadway, Suite 650 Santa Ana, CA 92706 714-541-3000	

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[X] (BY MAIL) I am familiar with the practice of Pacific Trial Attorneys for collection and processing of correspondence for mailing with the United States Postal Service. Correspondence so collected and processed is deposited with the United States Postal Service that same day in the ordinary course of business. On this date, a copy of said document was placed in a sealed envelope, with postage fully prepaid, addressed as set forth herein, and such envelope was placed for collection and mailing at Pacific Trial Attorneys, Newport Beach, California, following ordinary business practices.

[X] (FEDERAL) I declare that I am employed in the offices of a member of this Court at whose direction the service was made.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that this Certificate is executed on October 28, 2016, at Newport Beach, California.

Mandy K. Jung

EXHIBIT 1

AU029
00012

CAC

MARTIN E. JERISAT (273770)
E: mjeristat@fortheplaintiff.net
A: 2373 Morse Ave., Suite 322
Irvine, CA 92614
P: (714) 571-5700

GORDON G. PHILLIPS (90232)
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A: 1600 North Broadway, Suite 650
Santa Ana, CA 92706
P: (714) 541-3000

Counsel for Plaintiff and the Proposed Class

FILED
Superior Court of California
County of Los Angeles
SEP 26 2016
Sherri R. Carter, Executive Officer/Clerk
By Nancy Alvarez Deputy

D CCW 311 Shepard Wiley JR.

SUPERIOR COURT OF THE STATE OF CALIFORNIA
COUNTY OF LOS ANGELES

MOHAMMED DABOUSSI, on behalf of himself, all others similarly situated, and the general public,

Plaintiff,

v.

IOVATE HEALTH SCIENCES U.S.A., INC., and DOES 1-10,

Defendants.

Case No: BC635205

CLASS ACTION

COMPLAINT FOR:

VIOLATIONS OF CAL. BUS. & PROF. CODE §§17200 *et seq.*; CAL. BUS. & PROF. CODE §§17500 *et seq.*; CAL. CIV. CODE §§ 1750 *et seq.*; and BREACH OF EXPRESS & IMPLIED WARRANTIES

DEMAND FOR JURY TRIAL

CIT/CASE: BC635205
LEA/DEF#:
RECEIPT #: CCH451233059
DATE PAID: 09/26/16 03:02 PM
PAYMENT: $1,000.00
RECEIVED: 310
CHECK: $1,000.00
CASH: $0.00
CHANGE: $0.00
CARD: $0.00

CIT/CASE: BC635205
LEA/DEF#:
RECEIPT #: CCH451233058
DATE PAID: 09/26/16 03:01 PM
PAYMENT: $435.00
RECEIVED: 310
CHECK: $435.00
CASH: $0.00
CHANGE: $0.00
CARD: $0.00

Plaintiff Mohammed Daboussi, on behalf of himself, all others similarly situated, and the general public, by and through his undersigned counsel, hereby sues defendants Iovate Health Sciences U.S.A, Inc., and Does 1-10 (hereinafter "Defendants") and alleges the following upon his own knowledge, or where he lacks personal knowledge, upon information and belief, including the investigation of his counsel.

INTRODUCTION

1. Defendants manufacture and sell a line of weight loss dietary supplements marketed as scientifically shown to promote weight loss. These supplements include Garcinia Cambogia Plus, Garcinia Cambogia Plus Gummies, Coconut Oil, Green Coffee Bean, Matcha Green Tea Plus, Probiotics Plus Weight Loss, Raspberry Ketones Plus, Konjac Root Plus, Xendarine Core, and Xendarine Ultimate (the "Weight Loss Products"). These claims, however, are false, misleading, deceptive, and unlawful.

2. Plaintiff brings this action on behalf of himself, others similarly situated, and the general public, to enjoin Defendants' false, misleading, and unlawful advertising of their Weight Loss Products, and to seek compensation for himself and the putative class.

JURISDICTION & VENUE

3. The California Superior Court has jurisdiction over this matter as a result of Defendants' violations of the California Business and Professions Codes, California Civil Codes, and California common law principles.

4. The aggregate monetary damages and restitution sought herein exceed the minimum jurisdictional limits for the Superior Court and will be established at trial, according to proof.

5. The California Superior Court also has jurisdiction in this matter because there is no federal question at issue, as the issues herein are based solely on California statutes and law.

6. The Court has personal jurisdiction over Defendants Iovate Health Sciences U.S.A, Inc., and Does 1-10, because it has purposely availed itself of the benefits and privileges of conducting business activities within California.

7. Venue is proper in Los Angeles County because plaintiff resides in Los Angeles, and a substantial part of the events or omissions giving rise to the claims occurred in Los Angeles.

PARTIES

8. Plaintiff Mohammed Daboussi is a resident of Los Angeles, California.

9. Defendant Iovate Health Sciences U.S.A., Inc., (herein "Iovate"), is a Delaware corporation located at 1105 North Market Street, Suite 1330, Wilmington, Delaware 19801. Iovate Health Sciences, U.S.A., Inc. is the American subsidiary of Iovate Health Sciences, Inc., and is responsible for the manufacture, distribution, and marketing of weight loss products throughout the United States.

10. The Weight Loss Products have one key ingredient, green coffee bean extract. Coffee beans generally contain quinic acid esterified with p-coumaric, caffeic, and ferulic acid. Esterification produces at least 13 compounds, collectively called chlorogenic acids.

11. Does 1-10 are unknown to Plaintiff, but at all times were agents, servants, or employees of Defendants, and were at all times acting within the course and scope of their agency or employment, with Defendants' permission and consent. Each Doe defendant was and is in some way responsible for, participated in, or contributed to the conduct complained of herein, and subject to liability therefore. When Plaintiff ascertains the exact nature and identity of such Does, Plaintiff will seek leave of Court to amend this Complaint to set forth the same, with proper charging allegations.

FACTS

I. IOVATE'S DIETARY SUPPLEMENTS BUSINESS

12. Defendants manufacture and sell weight loss dietary supplements to major retailers in the U.S.

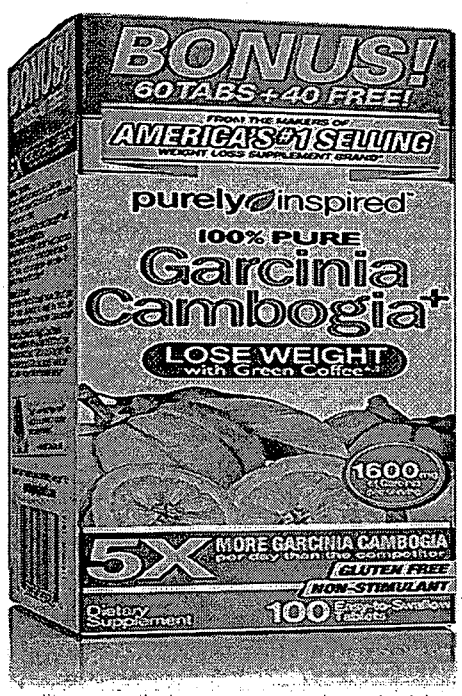
13. Dietary supplements are a multi-billion dollar industry in the United States.

14. Defendants are no strangers to false and/or misleading advertisements. For example, in 2010, The Federal Trade Commission sued Defendants for false and deceptive advertisement in the sale of dietary supplements.

15. As part of the settlement, Defendants agreed to pay a fine, and agreed to an injunction prohibiting them from making false or misleading advertising for weight loss supplements unless at the time of making such representation, Defendants possess competent and reliable scientific evidence consisting of *at least* ***two*** *adequate and well-controlled human clinical studies* of the advertised weight loss supplements (Exh. 1.)

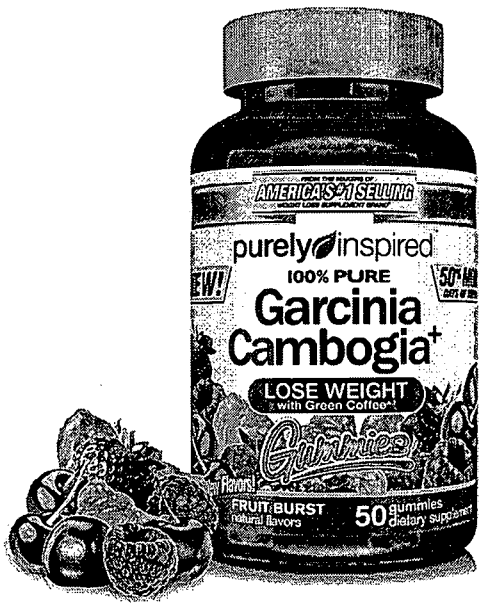
16. Because of the competitive nature of weight loss market, Defendants chose to make false and misleading claims about their Weight Loss Products to stand out in the crowd, and to increase their sales. Defendants advertised and sold eight Weight Loss Products enhanced by green coffee bean as the key ingredient to weight loss. These products include:

A. Garcinia Cambogia Plus;



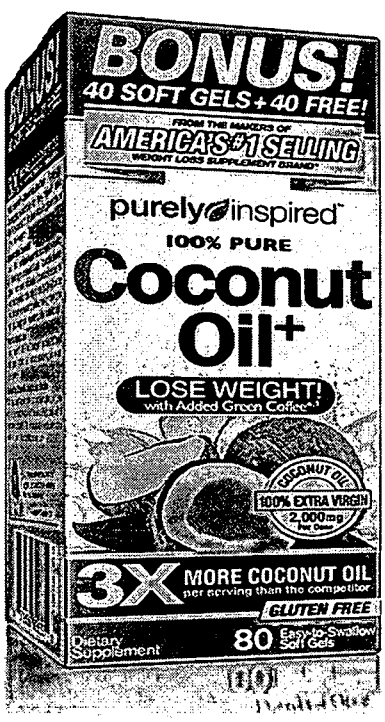
"LOSE WEIGHT with Green Coffee"

B. Garcinia Cambogia Plus Gummies;



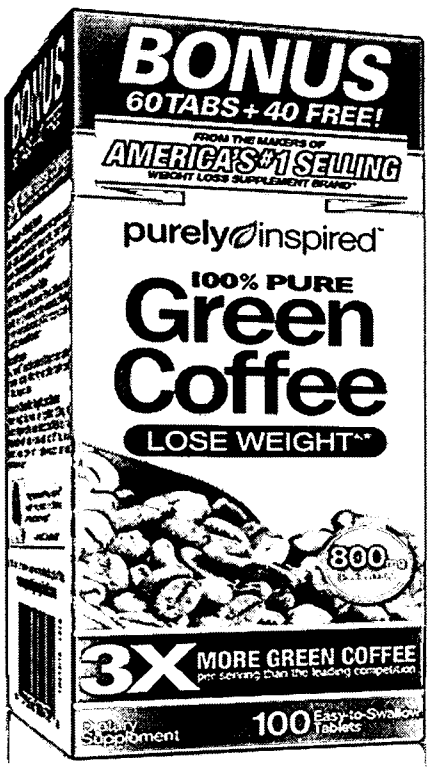
"LOSE WEIGHT with Green Coffee"

C. Coconut Oil;



"LOSE WEIGHT with Added Green Coffee"

D. Green Coffee Bean;

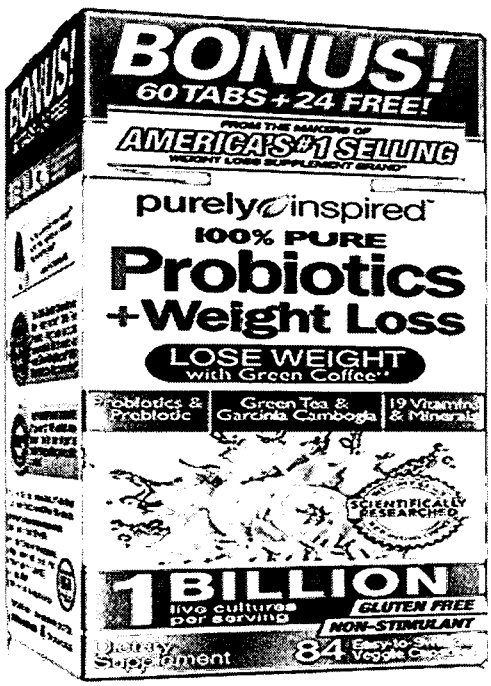


"LOSE WEIGHT"

E. Matcha Green Tea Plus;

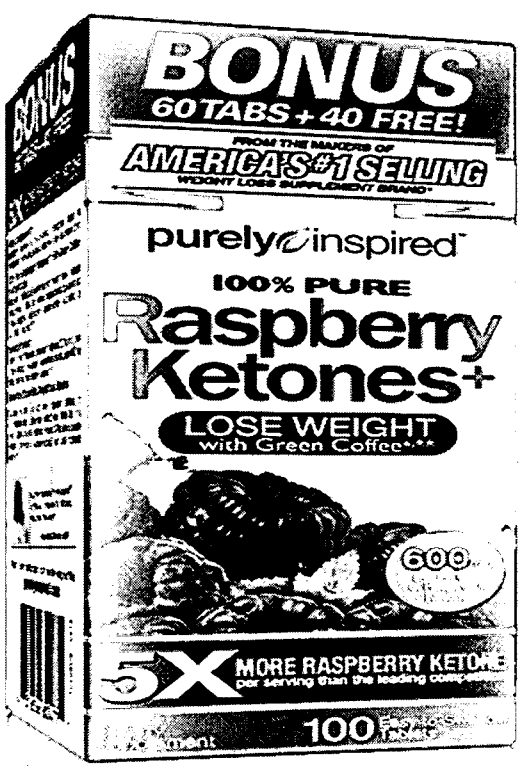
"LOSE WEIGHT with Green Coffee"

F. Probiotics Plus Weight Loss;



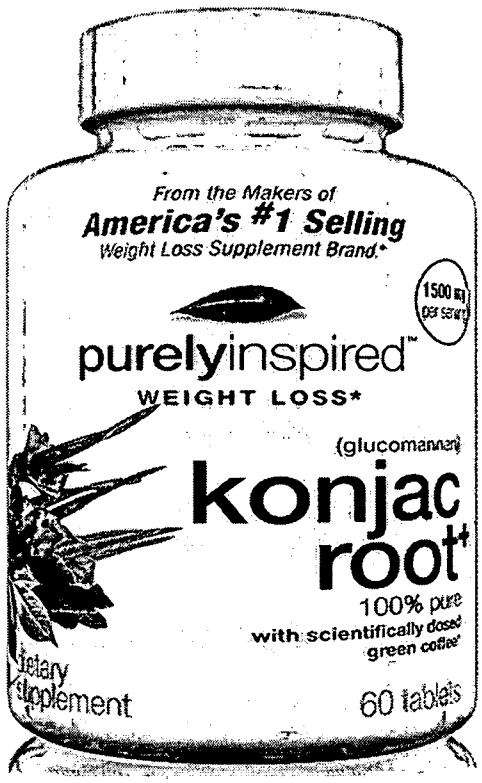
"LOSE WEIGHT with Green Coffee"

G. Raspberry Ketones Plus;



"LOSE WEIGHT with Green Coffee"

H. Konjac Root Plus;

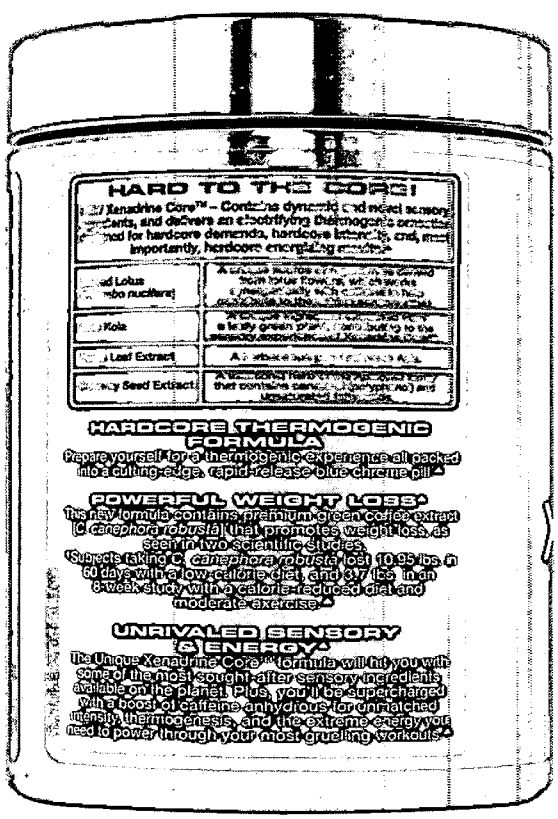


"WEIGHT LOSS with scientifically dosed green coffee"

I. Xendadrine Core; and

"POWERFUL WEIGHT LOSS"

J. Xenadrine Ultimate.



"WEIGHT LOSS SCIENTIFICALLY RESEARCHED INGREDIENT"

17. Regardless of the product, the label of the Weight Loss Products advertised loss of weight with Green Coffee. Examples of claims that have appeared on the Weight Loss Products labels include:

a. "LOSE WEIGHT with Green Coffee,"

b. "LOSE WEIGHT with added Green Coffee,"

c. "LOSE WEIGHT,"

d. "WEIGHT LOSS with scientifically dosed green coffee,"

e. "Lose Weight – It Really Works!,"

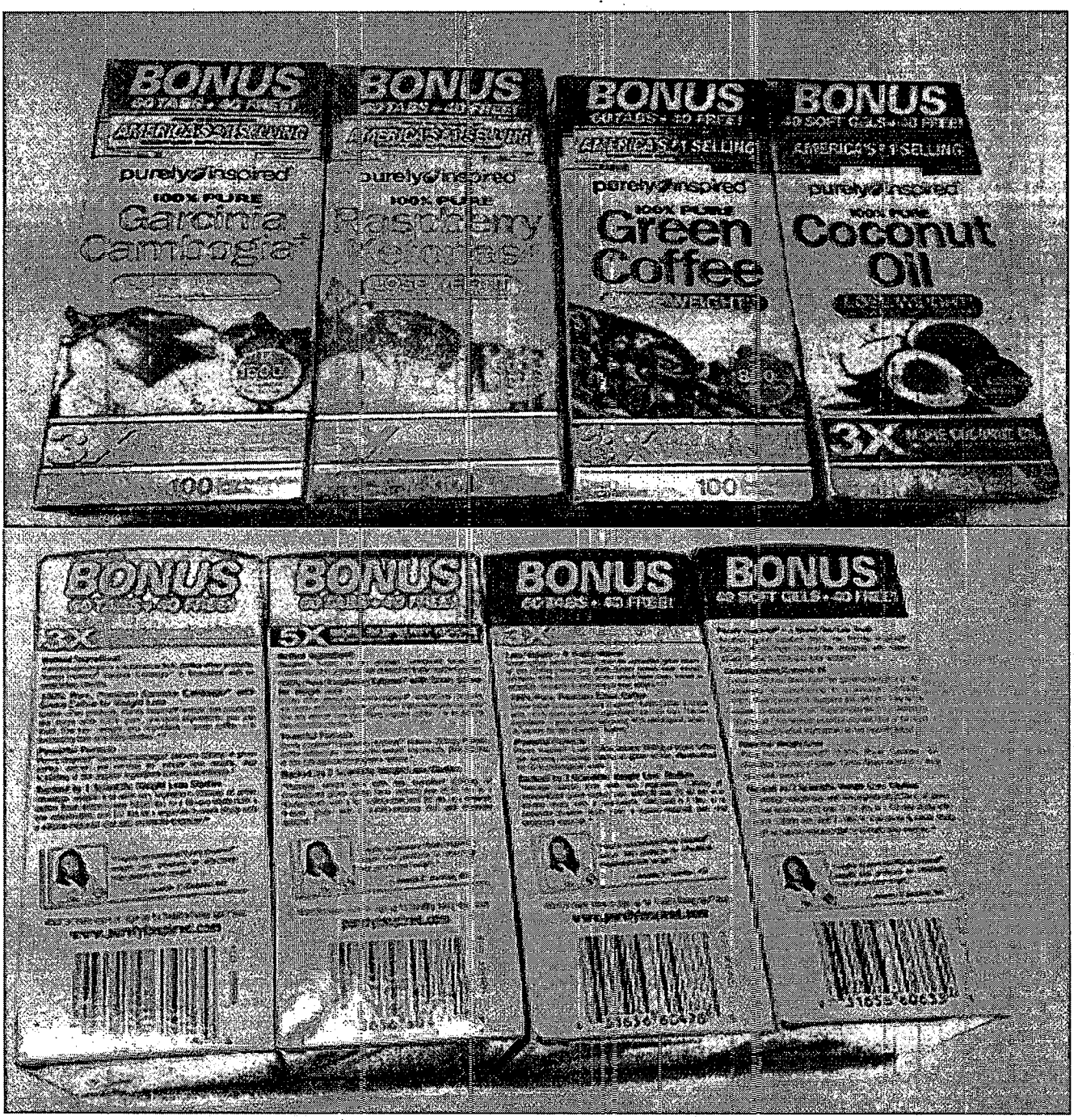
f. Green Coffee extract contains 45% chlorogenic acid, which has been shown in scientific research to help people lose weight,"

g. "Powerful Formula,"

h. "Backed by 2 Scientific Weight Loss Studies,"

i. "Average weight loss with key ingredient (200 mg of standardized green coffee bean extract) was **10.95 lbs.** in a **60-day** study with a low-calorie diet, and **3.7 lbs**. in a separate **8-week** study with a calorie-reduced diet and moderate exercise," and

j. "This new formula contains premium green coffee extract [C. canephora robusta] that promotes weight loss, as seen in two scientific studies. Subjects taking C. canaephora robusta lost **10.85 lbs**. in **60 days** with a low calorie-diet, and **3.7 lbs**. in an **8-week** study with a calorie-reduced diet and moderate exercise." (Emphasis added.)



18. The scientific study that Defendants referenced on the label is a four page summary report, prepared by two employees of the company that supplies Svetol, the active ingredient in Iovate Weight Loss Products (hereinafter "Summary Report") (Exh. 2.), (www.purelyinspired.com/wp-content/uploads/2016/02/Dellalibera_2006.pdf).

19. The Summary Report claims that fifty volunteers, aged 19 to 75, were divided into two groups. One group, with thirty volunteers, was asked to take one capsule of Svetol twice a day with main meal, and the other group, with twenty volunteers, was given a

placebo. All volunteers were considered overweight because each had a Body Mass Index (BMI) above 25, and were homogenous in weight and muscle mass/fat ratio (MM/FM). *Ibid.* at. p.2.

20. The Summary Report claims that volunteers were given one Svetol or placebo capsule with main meal twice a day, for sixty (60) days. *Ibid.*

21. The volunteers followed bland low caloric diet with no details about the diet or compliance with the diet. *Ibid.*

22. The following variables were gathered at the beginning of the study: age, height, sex, weight, BMI, MM/FM ratio, and self-evaluation of physical aspects. *Ibid.*

23. An evaluation of compliance and verification of the presence of side effects was undertaken after thirty days and sixty days. *Ibid.* at p.2.

24. According to the Summary Report, after sixty (60) days of treatment, a mean reduction in weight of **10.95 lbs. plus or minus 0.70 lbs. (a range of 11.61 to 10.25**) was observed in the group that took Svetol. *Ibid.*

25. The mean weight reduction in the placebo group, was **5.40 lbs. plus or minus 0. 81 lbs. (a range of 6.22 to 4.59**). *Ibid.*

26. The MM/FM ratio in the group that took Svetol increased compared to the control group by 4.1 plus or minus 0.7 versus 1.6 plus or minus 0.6. The mean weight reduction and increase in MM/FM ratio were statistically significant. *Ibid.*

27. Some of the flaws in the Summary Report include:

a. The Summary Report provided no data showing reduction in weight and/or increase in MM/FM of the volunteers.

b. The Summary Report provided no baseline body weight or MM/FM for the volunteers.

c. The Summary Report did not provide the percentage of chlorogenic acid in the green coffee extract.

d. The Summary Report did not provide any data about randomization, double-blindness and/or placebo control of any of the studies.

e. The Summary Report did not report on any controls of life style factors.

f. The Summary Report did not describe whether investigators or participants were blinded to treatment assignment.

g. The Summary Report did not address the goals of the study, overweight, obesity, and metabolic conditions.

h. The authors of the Summary Report did not follow up with the subjects to determine whether the loss of weight was temporary.

i. There was nothing in the Summary Report that suggests that people with BMI less than 25 can benefit from Svetol.

j. The authors of the Summary Report did not disclose or disclaim any conflict of interests, even though both were employed by the company that makes Svetol supplement.

II. DEFENDANTS' WEIGHT LOSS CLAIMS ARE FALSE, MISLEADING, DECEPTIVE, AND UNLAWFUL

28. Weight loss of **10.95 lbs. in a 60-day** study with a low calorie diet.

Defendants represent on their labels that volunteers lost an average of 10.95 lbs. when they used the Weight Loss Products for 60 days as shown by the Summary Report. This representation is false, misleading, deceptive, and unlawful because Defendants concealed the fact that the volunteers who used the Svetol product lost a mean of 10.95 lbs. **compared to those who used a placebo who lost a mean of 5.40 lbs**. In other words, volunteers who used the Svetol product lost half the weight claimed by the label, about 5 lbs. when compared to the control group. Furthermore, volunteers lost 5.40 lbs. without taking any Weight Loss Products.

29. Weight loss of **3.7 lbs**. in **a separate** 8-week study with a calorie-reduced diet and moderate exercise.

Defendants represent on their labels that volunteers lost an average of 3.7 lbs. when they used the Weight Loss Products for 8-weeks as shown by a scientific study. This representation is false, misleading, deceptive, and unlawful because there was no separate

study, but the same Summary Report about volunteers who took Svetol for 60 days or 8 weeks. Further, there is nothing in the Summary Report about volunteers losing 3.7 lbs. anywhere.

30. Backed by 2 Scientific Weight Loss Studies.

Defendants represent on their label that there are two scientific studies that support weight loss claims of volunteers who used green coffee bean. This statement is false, deceptive, misleading, and unlawful because Defendants' website references only one study ("SummaryReport")(http://www.purelyinspired.com/wpcontent/uploads/2016/02/Dellaliber a_2006.pdf). *Ibid.*

31. There is Ample Evidence Against Green Coffee Bean Extract.

There is ample scientific evidence that Defendants' claims regarding the efficacy of green coffee bean extract for weight loss, are false, misleading, deceptive, and unlawful. One study in the Journal of Agricultural and Food Chemistry, assessed the effect of chlorogenic acid supplementation, the main ingredient in Svetol, on diet-induced obesity, glucose intolerance, insulin resistance and signaling pathways. The study found that the chlorogenic acid was not effective when given to mice over a 12-week period. *Supplementation of a High-Fat Diet with Chlorogenic Acid Is Associated with Insulin Resistance and Hepatic Lipid Accumulation in Mice*, 61 J. AGRIC. FOOD CHEM. 4371–4378 (2013)(Exh. 3.)

Another study reviewed the current literature on green coffee for the use of weight loss, which is limited to four small studies. The review found that claims regarding efficacy of green coffee bean extract for weight loss were false because these studies have significant limitations, including lack of blinding, direct comparison, very low sample size, and none assessed whether weight was regained on discontinuation. *Green Coffee for Pharmacological Weight Loss*, **Journal of Evidence-Based Complimentary & Alternative Medicine** 18(4) 309-313 (2013)(Exh. 4.)

Likewise, two additional meta reviews concluded that these studies have significant limitations. *The Use of Green Coffee Extract as a Weight Loss Supplement: A Systematic*

Review and Meta-Analysis of Randomized Clinical Trials, **Gastroenterology Research and Practice**, Volume 2011, (Exh. 5); and *Supplements for Weight Loss: Hype or Help for Obesity? Part II. The Inside Scoop on Green Coffee Bean Extract*? **Nutrition in Clinical Practice**, Volume 30 Number 20 (2015)(Exh. 6.)

Furthermore, the **European Food Safety Authority** has concluded in a published opinion that there is no cause and effect relationship between consumption of chlorogenic acids from coffee and contribution to the maintenance or achievement of a normal body weight (Exh. 7.)

CLASS ACTION ALLEGATIONS

33. California Code of Civil Procedure section 382 provides that "when the question is one of a common or general interest, of many persons, or when the parties are numerous, and it is impracticable to bring them all before the court, one or more may sue or defend for the benefit of all."

34. While reserving the right to redefine or amend the class definition prior to seeking class certification, Plaintiff brings this suit as a class action pursuant to Cal. Code Civ. P. § 382 on behalf of himself and a Class of all persons in California who in the past four years (the "Class Period"), purchased, for personal or household use, and not for resale or distribution purposes, any of the Weight Loss Products.

35. The members in the proposed Class are so numerous that individual joinder of all members is impracticable, and the disposition of the claims of all Class Members in a single action will provide substantial benefits to the parties and Court.

36. Questions of law and fact common to Plaintiff and the Class include:

a. whether Defendants communicated a message regarding weight loss benefits of their Weight Loss Products through their packaging and advertising;

b. whether that message was material, or likely to be material to a reasonable consumer;

c. whether the health and benefit claims are false, misleading, or reasonably likely to deceive a reasonable consumer;

d. whether Defendants' conduct violates public policy;

e. whether Defendants' conduct violates state or federal food statutes or regulations;

f. the proper amount of damages, including punitive damages;

g. the proper amount of restitution;

h. the proper scope of injunctive relief; and

i. the proper amount of attorneys' fees.

37. These common questions of law and fact predominate over questions that affect only individual Class Members.

38. Plaintiff's claims are typical of Class Members' claims because they are based on the same underlying facts, events, and circumstances relating to Defendants' conduct. Specifically, all Class Members, including Plaintiff, were subjected to the same misleading and deceptive conduct when they purchased the challenged Weight Loss Products, and suffered economic injury because the Weight Loss Products are misrepresented. Absent Defendants' business practice of deceptively and unlawfully labeling its products, Plaintiff and Class members would not have purchased the Weight Loss Products.

39. Plaintiff will fairly and adequately represent and protect the interests of the Class, has no interests incompatible with the interests of the Class, and has retained counsel competent and experienced in class action litigation, and specifically in litigation involving the false and misleading advertising of foods and dietary supplements.

40. Class treatment is superior to other options for resolution of the controversy because the relief sought for each Class Member is small such that, absent representative litigation, it would be infeasible for Class Members to redress the wrongs done to them.

41. Questions of law and fact common to the Class predominate over any questions affecting only individual Class Members.

42. Defendants have acted on grounds applicable to the Class, thereby making appropriate final injunctive and declaratory relief concerning the Class as a whole.

CAUSES OF ACTION

FIRST CAUSE OF ACTION

Violations of the Unfair Competition Law,

Cal. Bus. & Prof. Code §§ 17200 *et seq.*

43. Plaintiff realleges and incorporates the allegations elsewhere in the Complaint as if set forth in full herein.

44. The UCL prohibits any "unlawful, unfair or fraudulent business act or practice." Cal. Bus. & Prof. Code §17200.

45. The acts, omissions, misrepresentations, practices, and non-disclosures of Defendants as alleged herein constitute business acts and practices.

Fraudulent

46. A statement or practice is fraudulent under the UCL if it is likely to deceive the public, applying a reasonable consumer test.

47. As set forth herein, the Defendants' claims relating to the Weight Loss Products are likely to deceive reasonable consumers and the public.

Unlawful

48. The acts alleged herein are "unlawful" under the UCL in that they violate at least the following laws:

- The False Advertising Law, Cal. Bus. & Prof. Code §§ 17500 *et seq.*;
- The Consumers Legal Remedies Act, Cal. Civ. Code §§ 1750 *et seq.*;

Unfair

49. Defendants' conduct with respect to the labeling, advertising, and sale of the Weight Loss products was unfair because Defendants' conduct was immoral, unethical, unscrupulous, or substantially injurious to consumers and the utility of their conduct, if any, does not outweigh the gravity of the harm to their victims.

50. Defendants' conduct with respect to the labeling, advertising, and sale of the Weight Loss Products was also unfair because it violated public policy as declared by specific constitutional, statutory or regulatory provisions, including but not limited to the False Advertising Law.

51. Defendants' conduct with respect to the labeling, advertising, and sale of the Weight Loss Products was also unfair because the consumer injury was substantial, not outweighed by benefits to consumers or competition, and not one consumers themselves could reasonably have avoided.

52. Defendants concealed material information about the sole Summary Report that supports its claims about the weight loss benefits of its products to deceive the consuming public into purchasing its Weight Loss Products.

53. Defendants profited from their sales of the falsely, deceptively, and unlawfully advertised the Weight Loss Products to unwary consumers.

54. Plaintiff and Class Members are likely to be damaged by Defendants' deceptive trade practices, as Defendants continue to disseminate misleading information. Thus, injunctive relief enjoining this deceptive practice is proper.

55. Defendants' conduct caused and continues to cause substantial injury to Plaintiff and the other Class Members. Plaintiff has suffered injury in fact as a result of Defendants' unlawful conduct.

56. In accordance with Bus. & Prof. Code § 17203, Plaintiff seeks an order enjoining Defendants from continuing to conduct business through unlawful, unfair, and/or fraudulent acts and practices, and to commence a corrective advertising campaign.

SECOND CAUSE OF ACTION

Violations of the False Advertising Law,

Cal. Bus. & Prof. Code §§ 17500 *et seq.*

57. Plaintiff realleges and incorporates the allegations elsewhere in the Complaint as if set forth in full herein.

58. Under the FAL, "[i]t is unlawful for any person, firm, corporation or association, or any employee thereof with intent directly or indirectly to dispose of real or personal property or to perform services" to disseminate any statement "which is untrue or misleading, and which is known, or which by the exercise of reasonable care should be known, to be untrue or misleading." Cal. Bus. & Prof. Code § 17500.

59. It is also unlawful under the FAL to disseminate statements concerning property or services that are "untrue or misleading, and which is known, or which by the exercise of reasonable care should be known, to be untrue or misleading." *Id.*

60. As alleged herein, the advertisements, labeling, policies, acts, and practices of defendants relating to the Weight Loss Products misled consumers acting reasonably as to the healthfulness of the products.

61. Plaintiff suffered injury in fact as a result of Defendants' actions as set forth herein because Plaintiff purchased Weight Loss Products in reliance on Defendants' false and misleading marketing claims that these products have been shown scientifically to help consumers lose weight.

62. Defendants' business practices as alleged herein constitute unfair, deceptive, untrue, and misleading advertising pursuant to the FAL because defendants have advertised the Weight Loss Products in a manner that is untrue and misleading, which defendants knew or reasonably should have known, and omitted material information from the products' advertising.

63. Defendants profited from their sales of the falsely and deceptively advertised Weight Loss Products to unwary consumers.

64. As a result, pursuant to Cal. Bus. & Prof. Code § 17535, Plaintiff and the Class are entitled to injunctive and equitable relief.

THIRD CAUSE OF ACTION

Violations of the Consumer Legal Remedies Act,

Cal. Civ. Code §§ 1750 *et seq.*

65. Plaintiff realleges and incorporates the allegations elsewhere in the Complaint as if set forth in full herein.

66. The CLRA prohibits deceptive practices in connection with the conduct of a business that provides goods, property, or services primarily for personal, family, or household purposes.

67. Defendants' false and misleading labeling and other policies, acts, and practices were designed to, and did, induce the purchase and use of the Weight Loss Products for personal, family, or household purposes by Plaintiff and Class Members, and violated and continue to violate the following sections of the CLRA:

a. § 1770(a)(5): representing that goods have characteristics, uses, or benefits which they do not have;

b. § 1770(a)(7): representing that goods are of a particular standard, quality, or grade if they are of another;

c. § 1770(a)(9): advertising goods with intent not to sell them as advertised; and

d. § 1770(a)(16): representing the subject of a transaction has been supplied in accordance with a previous representation when it has not.

68. Defendants profited from their sales of the falsely, deceptively, and unlawfully advertised their Weight Loss Products to unwary consumers.

69. Defendants' wrongful business practices constituted, and constitute, a continuing course of conduct in violation of the CLRA.

70. As a result, Plaintiff and the Class have suffered harm, and therefore seek restitution and injunctive relief in the form of modified advertising and a corrective advertising plan.

71. In compliance with Cal. Civ. Code § 1782, plaintiff has sent written notice to Defendants of his claims. Although Plaintiff does not currently seek damages for his claims under the CLRA, if Defendants refuse to remedy the violation within 30 days of receiving the letter, Plaintiff may thereafter amend this Complaint to seek damages.

72. In compliance with Cal. Civ. Code § 1780(d), Plaintiff's venue affidavit is filed concurrently herewith.

FOURTH CAUSE OF ACTION

Breach of Express Warranties,

Cal. Comm. Code § 2313(1)

73. Plaintiff realleges and incorporates the allegations elsewhere in the Complaint as if set forth in full herein.

74. Through the Weight Loss Products' labels, Defendants made affirmations of fact or promises, or description of goods, which were "part of the basis of the bargain," in that Plaintiff and the Class purchased the products in reasonable reliance on those statements. Cal. Com. Code § 2313(1).

75. Defendants breached their express warranties by selling products that do not support weight loss.

76. That breach actually and proximately caused injury in the form of the lost purchase price that plaintiff and Class members paid for the Weight Loss Products.

77. As a result, Plaintiff seeks, on behalf of himself and other Class Members, injunctive relief prohibiting Defendants from continuing false and misleading advertisement.

78. Prior to filing the lawsuit, Plaintiff, on behalf of himself and the class, gave Defendants notice of the breach.

FIFTH CAUSE OF ACTION

Breach of Implied Warranty of Merchantability,

Cal. Comm. Code § 2314

79. Plaintiff realleges and incorporates the allegations elsewhere in the Complaint as if set forth in full herein.

80. Defendants, through their acts and omissions set forth herein, in the sale, marketing and promotion of the Weight Loss Products, made representations to Plaintiff and the Class that, among other things, the products promote weight loss.

81. Plaintiff and the Class bought the Weight Loss Products manufactured, advertised, and sold by Defendants, as described herein.

82. Defendants are merchants with respect to the goods of this kind which were sold to Plaintiff and the Class, and there was, in the sale to Plaintiff and other consumers, an implied warranty that those goods were merchantable.

83. However, Defendants breached that implied warranty in that the Weight Loss Products do not promote weight loss.

84. As an actual and proximate result of Defendants' conduct, Plaintiff and the Class did not receive goods as impliedly warranted by Defendants to be merchantable in that they did not conform to promises and affirmations made on the container or label of the goods.

85. Plaintiff and Class have sustained damages as a proximate result of the foregoing breach of implied warranty in the amount of the Weight Loss Products' purchase price.

86. Prior to filing the lawsuit, plaintiff, on behalf of himself and the class, gave Defendants notice of the breach.

PRAYER FOR RELIEF

87. Wherefore, Plaintiff, on behalf of himself, all others similarly situated and the general public, prays for judgment against Defendants as to each and every cause of action, and the following remedies:

A. An Order declaring this action to be a proper class action, appointing Plaintiff as class representative, and appointing undersigned counsel as class counsel;

B. An Order requiring Defendants to bear the cost of class notice;

C. An Order enjoining Defendants from using any challenged labeling or marketing claim that is found to be false, misleading, or unlawful;

D. An Order compelling Defendants to conduct a corrective advertising campaign;

E. An Order compelling Defendants to destroy all misleading and deceptive advertising materials and the Weight Loss Products' labels;

F. An Order requiring Defendants to disgorge or return all monies, revenues, and profits obtained by means of any wrongful or unlawful act or practice;

G. An Order requiring Defendants to pay restitution to restore all funds acquired by means of any act or practice declared by this Court to be an unlawful, unfair, or fraudulent business act or practice, untrue or misleading advertising, or a violation of the UCL, FAL, or CLRA, plus pre- and post-judgment interest thereon;

H. An Order requiring Defendants to pay Plaintiff's costs, expenses, and reasonable attorneys' fees; and

I. Any other and further relief that Court deems necessary, just, or proper.

JURY DEMAND

Plaintiff hereby demands a trial by jury on all triable issues.

Dated: September 23, 2016

/s/Martin E. Jerisat
2373 Morse Ave., Ste. 322,
Irvine, CA 92614
P: (714) 571-5700
Attorneys for Plaintiff and the Proposed Class

EXHIBIT 1

EXHIBIT 1

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ATTORNEYS FOR PLAINTIFF
FEDERAL TRADE COMMISSION

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF NEW YORK

FEDERAL TRADE COMMISSION, Plaintiff, v. **IOVATE HEALTH SCIENCES USA, INC.**, et al., Defendants.

CASE NO. 10-CV-587

STIPULATED FINAL JUDGMENT AND ORDER FOR PERMANENT INJUNCTION AND OTHER EQUITABLE RELIEF

Plaintiff, the Federal Trade Commission ("Commission" or "FTC"), filed a Complaint for Permanent Injunction and Other Equitable Relief against corporations, Iovate Health Sciences USA, Inc., Iovate Health Sciences, Inc., and Iovate Health Sciences Group, Inc., n/k/a Kerr Investment Holding Corp., pursuant to Section 13(b) of the Federal Trade Commission Act ("FTC Act"), 15 U.S.C. § 53(b), alleging deceptive acts or practices and false advertisements in violation of Sections 5(a) and 12 of the FTC Act, 15 U.S.C. §§ 45(a) and 52.

The Commission and Defendants have stipulated to the entry of this Order in settlement of the Commission's allegations against Defendants. The Court, having been presented with this Stipulated Final Judgment and Order for Permanent Injunction and Other Equitable Relief ("Order"), finds as follows:

FINDINGS

1. This Court has jurisdiction over the subject matter of this case and, pursuant to the Stipulation in Paragraph 4 below, jurisdiction over all parties. Venue in the United States District Court for the Western District of New York is proper.

2. The Complaint states a claim upon which relief can be granted, and the Commission has the authority to seek the relief it has requested.

3. The activities of Defendants, for purposes of this Order, are in or affecting commerce, as defined in Section 4 of the FTC Act, 15 U.S.C. § 44.

4. The Commission and Defendants stipulate and agree to entry of this Order under Section 13(b) of the FTC Act, 15 U.S.C. § 53(b), without trial or final adjudication of any issue of fact or law. By entering into this stipulation, Defendants do not admit or deny any of the allegations set forth in the Complaint, other than jurisdictional facts, to which Defendants are stipulating only as to this action and subsequent actions arising from this action, including enforcement and modification of this Order.

5. Defendants waive all rights to seek judicial review or otherwise challenge or contest the validity of this Order. Defendants also waive any claim that they may have held under the Equal Access to Justice Act, 28 U.S.C. § 2412, concerning the prosecution of this action to the date of this Order.

6. This action and the relief awarded herein are in addition to, and not in lieu of,

other remedies as may be provided by law.

7. Pursuant to Federal Rule of Civil Procedure 65(d), the provisions of this Order are binding upon Defendants, and their officers, agents, servants, representatives, employees, and all other persons or entities in active concert or participation with them, who receive actual notice of this Order by personal service or otherwise.

8. This Order reflects the negotiated agreement of the parties.

9. The parties shall jointly be deemed to be the drafters of this Order; the rule that any ambiguity in a contract shall be construed against the drafter of the contract shall not apply to this Order.

10. Nothing in this Order obviates the obligation of Defendants to comply with Sections 5 and 12 of the FTC Act, 15 U.S.C. §§ 45 and 52.

11. The Commission's action against Defendants is an exercise of the Commission's police or regulatory power as a governmental unit.

12. The paragraphs of this Order shall be read as the necessary requirements of compliance and not as alternatives for compliance, and no paragraph serves to modify another paragraph unless expressly so stated.

13. Each party shall bear its own costs and attorneys' fees.

14. Entry of this Order is in the public interest.

ORDER

DEFINITIONS

Unless otherwise specified,

1. "Defendants" means Iovate Health Sciences USA, Inc., Iovate Health Sciences,

Inc., and Iovate Health Sciences Group, Inc., n/k/a Kerr Investment Holding Corp., and their successors and assigns.

2. "Iovate Products" means, collectively, Cold MD, Germ MD EZ-Swallow Rapid-Tabs, Germ MD Effervescent Tablets, Allergy MD, Allergy MD Rapid-Tabs, nanoSLIM, and Accelis.

3. "Commerce" means as defined in Section 4 of the FTC Act, 15 U.S.C. § 44.

4. "Adequate and well-controlled human clinical study" means a human clinical study that is randomized, double-blind, placebo-controlled, and conducted by persons qualified by training and experience to conduct such study.

5. "Covered Product" means any dietary supplement, food, or drug, including, but not limited to, the Iovate Products.

6. "Essentially Equivalent Product" means a product that contains the identical ingredients, except for inactive ingredients (e.g., binders, colors, fillers, excipients), in the same form and dosage, and with the same route of administration (e.g., orally, sublingually), as the covered product; *provided that* the Covered Product may contain additional ingredients if reliable scientific evidence generally accepted by experts in the field demonstrates that the amount and combination of additional ingredients is unlikely to impede or inhibit the effectiveness of the ingredients in the Essentially Equivalent Product.

7. "Endorsement" means as defined in 16 C.F.R. § 255.0(b).

8. "Food" and "drug" means as defined in Section 15 of the FTC Act, 15 U.S.C. § 55.

9. "Dietary supplement" means:

a. any product labeled as a dietary supplement or otherwise represented as a dietary supplement; or

b. any pill, tablet, capsule, powder, softgel, gelcap, liquid, or other similar form containing one or more ingredients that are a vitamin, mineral, herb or other botanical, amino acid, probiotic, or other dietary substance for use by humans to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above, that is intended to be ingested, and is not represented to be used as a conventional food or as a sole item of a meal or the diet.

10. The term "including" in this Order means "including without limitation."

11. The terms "and" and "or" in this Order shall be construed conjunctively or disjunctively as necessary, to make the applicable phrase or sentence inclusive rather than exclusive.

I.

PROHIBITED REPRESENTATIONS: DISEASE CLAIMS

IT IS HEREBY ORDERED that Defendants, directly or through any corporation, partnership, subsidiary, division, trade name, or other device, and their officers, agents, servants, representatives, employees, and all persons or entities in active concert or participation with them who receive actual notice of this Order, by personal service or otherwise, in connection with the manufacturing, labeling, advertising, promotion, offering for sale, sale, or distribution of any drug or dietary supplement, in or affecting commerce, are hereby permanently restrained and enjoined from making, or assisting others in making, directly or by implication, including

through the use of a product name, endorsement, depiction, or illustration, any representation that such product is effective in the diagnosis, cure, mitigation, treatment, or prevention of any disease, including, but not limited to, any representation that such product:

A. Reduces the risk, incidence, or frequency of colds or flu;

B. Prevents colds or flu;

C. Protects against colds or flu in crowded places;

D. Reduces the severity or duration of colds or flu;

E. Provides relief from hay fever; or

F. Provides relief (including fast or long-lasting relief) from seasonal, all-season, or environmental allergies;

unless the representation is non-misleading and such product: is subject to a final OTC drug monograph promulgated by the Food and Drug Administration (FDA) for such use, and conforms to the conditions of such use; remains covered by a tentative final OTC drug monograph for such use, and adopts the conditions of such use; or is the subject of a new drug application for such use approved by FDA, and conforms to the conditions of such use.

II.

PROHIBITED REPRESENTATIONS: WEIGHT-LOSS CLAIMS

IT IS FURTHER ORDERED that Defendants, directly or through any corporation, partnership, subsidiary, division, trade name, or other device, and their officers, agents, servants, representatives, employees, and all persons or entities in active concert or participation with them who receive actual notice of this Order, by personal service or otherwise, in connection with the manufacturing, labeling, advertising, promotion, offering for sale, sale, or distribution of any Covered Product, in or affecting commerce, are hereby permanently restrained and

enjoined from making, or assisting others in making, directly or by implication, including through the use of a product name, endorsement, depiction, or illustration, any representation that such product:

A. Causes weight loss; or

B. Causes rapid weight loss;

unless the representation is non-misleading and, at the time of making such representation, Defendants possess and rely upon competent and reliable scientific evidence that substantiates that the representation is true. For purposes of this Section, competent and reliable scientific evidence shall consist of at least two adequate and well-controlled human clinical studies of the Covered Product, or of an Essentially Equivalent Product, conducted by different researchers, independently of each other, that conform to acceptable designs and protocols and whose results, when considered in light of the entire body of relevant and reliable scientific evidence, are sufficient to substantiate that the representation is true. Defendants shall have the burden of proving that a product satisfies the definition of Essentially Equivalent Product.

III.

PROHIBITED REPRESENTATIONS: OTHER HEALTH-RELATED CLAIMS

IT IS FURTHER ORDERED that Defendants, directly or through any corporation, partnership, subsidiary, division, trade name, or other device, and their officers, agents, servants, representatives, employees, and all persons or entities in active concert or participation with them who receive actual notice of this Order, by personal service or otherwise, in connection with the manufacturing, labeling, advertising, promotion, offering for sale, sale, or distribution of any Covered Product, in or affecting commerce, are hereby permanently restrained and enjoined from making, or assisting others in making, directly or by implication, including

through the use of a product name, endorsement, depiction, or illustration, any representation, other than representations covered under Sections I or II of this Order, about the health benefits, performance, or efficacy of any Covered Product, other than claims regarding bodybuilding and exercise performance (e.g., increased muscle mass or body mass, increased strength and power, improved weight training performance, increased work-out intensity, improved muscle endurance, or improved muscle recovery), unless the representation is non-misleading, and, at the time of making such representation, Defendants possess and rely upon competent and reliable scientific evidence that is sufficient in quality and quantity based on standards generally accepted in the relevant scientific fields, when considered in light of the entire body of relevant and reliable scientific evidence, to substantiate that the representation is true. For purposes of this Section, competent and reliable scientific evidence means tests, analyses, research, or studies that have been conducted and evaluated in an objective manner by qualified persons and are generally accepted in the profession to yield accurate and reliable results.

IV.

PROHIBITED REPRESENTATIONS REGARDING TESTS OR STUDIES

IT IS FURTHER ORDERED that Defendants, directly or through any corporation, partnership, subsidiary, division, trade name, or other device, and their officers, agents, servants, representatives, employees, and all persons or entities in active concert or participation with them who receive actual notice of this Order, by personal service or otherwise, in connection with the manufacturing, labeling, advertising, promotion, offering for sale, sale, or distribution of any Covered Product, in or affecting commerce, are hereby permanently restrained and enjoined from misrepresenting, in any manner, expressly or by implication, including through the use of any product name or endorsement, the existence, contents, validity, results,

conclusions, or interpretations of any test or study, in connection with any representations covered by Sections I through III of this Order.

V.

PROHIBITED REPRESENTATIONS REGARDING HOMEOPATHIC DRUGS

IT IS FURTHER ORDERED that Defendants, directly or through any corporation, partnership, subsidiary, division, trade name, or other device, and their officers, agents, servants, representatives, employees, and all persons or entities in active concert or participation with them who receive actual notice of this Order, by personal service or otherwise, in connection with the manufacturing, labeling, advertising, promotion, offering for sale, sale, or distribution of any Covered Product, in or affecting commerce, are hereby permanently restrained and enjoined from making, or assisting others in making, directly or by implication, including through the use of a product name, endorsement, depiction, or illustration, any representation that such product is a homeopathic drug unless:

A. Such product is recognized as such by the *Homeopathic Pharmacopoeia of the United States*; and

B. The representation is true and not misleading.

VI.

FDA APPROVED CLAIMS

IT IS FURTHER ORDERED that nothing in this Order shall prohibit Defendants from making any representation for any product that is specifically permitted in labeling for such product by regulations promulgated by the Food and Drug Administration pursuant to the Nutrition Labeling and Education Act of 1990.

VII.

MONETARY JUDGMENT AND CONSUMER REDRESS

IT IS FURTHER ORDERED that:

A. Judgment is hereby entered in favor of the Commission and against Defendants in the amount of five million, five hundred thousand dollars ($5,500,000.00), which shall be paid to the Commission by electronic funds transfer within twenty (20) days of the date of entry of this Order and in accordance with instructions provided by the Commission.

B. In the event of default on any obligation to make payment under this Order, interest, computed pursuant to 28 U.S.C. § 1961(a), shall accrue from the date of default to the date of payment. In the event such default continues for ten (10) calendar days beyond the date that payment is due, the entire amount shall immediately become due and payable. Defendants shall be jointly and severally liable for all payments required by this Subsection and any interest on such payments.

C. All funds paid to the Commission pursuant to this Order shall be deposited into an account administered by the Commission or its agents to be used for equitable relief, including, but not limited to, consumer redress, and any attendant expenses for the administration of such equitable relief. In the event that direct redress to consumers is wholly or partially impracticable or funds remain after the redress to consumers is completed, the Commission may apply any remaining funds for such other equitable relief (including consumer information remedies) as it determines to be reasonably related to Defendants' practices alleged in the Complaint. Any funds not used for such equitable relief shall be deposited in the United States Treasury as disgorgement. Defendants shall have no right to challenge the Commission's choice of remedies under this Part. Defendants shall have no right to contest the manner of distribution chosen by

the Commission. No portion of any payment under the judgment herein shall be deemed a payment of any fine, penalty, or punitive assessment.

D. Defendants relinquish all dominion, control, and title to the funds paid to the fullest extent permitted by law. Defendants shall make no claim to or demand for return of the funds, directly or indirectly, through counsel or otherwise.

E. Defendants agree that the facts as alleged in the Complaint filed in this action shall be taken as true without further proof in any bankruptcy case or subsequent civil litigation pursued by the Commission to enforce its rights to any payment or money judgment pursuant to this Order, including, but not limited to, a nondischargeability complaint in any bankruptcy case. Defendants further stipulate and agree that the facts alleged in the Complaint establish all elements necessary to sustain an action pursuant to, and that this Order shall have collateral estoppel effect for purposes of, Section 523(a)(2)(A) of the Bankruptcy Code, 11 U.S.C. § 523(a)(2)(A). For all other purposes and with respect to all other parties, Defendants' stipulation in this Section shall have no effect. It is specifically agreed and acknowledged that this Section is not intended to be, nor shall it be, construed as an admission of liability by Defendants with respect to the allegations set forth in the Complaint with respect to any claims or demands by any third parties.

F. In accordance with 31 U.S.C. § 7701, Defendants are hereby required, unless they have done so already, to furnish to the Commission their taxpayer identifying numbers, which shall be used for the purposes of collecting and reporting on any delinquent amount arising out of Defendants' relationship with the government.

G. Proceedings instituted under this Part are in addition to, and not in lieu of, any other civil or criminal remedies that may be provided by law, including any other proceedings the Commission may initiate to enforce this Order.

VIII.

COMPLIANCE MONITORING

IT IS FURTHER ORDERED that, for the purpose of monitoring and investigating compliance with any provision of this Order.

A. Within ten (10) days of receipt of written notice from a representative of the Commission, Defendants shall submit additional written reports, which are true and accurate and sworn to under penalty of perjury; produce documents for inspection and copying; appear for deposition; and provide entry during normal business hours to any business location in Defendants' possession or direct or indirect control to inspect the business operation;

B. In addition, the Commission is authorized to use all other lawful means, including, but not limited to:

1. obtaining discovery from any person, without further leave of court, using the procedures prescribed by Fed. R. Civ. P. 30, 31, 33, 34, 36, 45 and 69; and

2. having its representatives pose as consumers and suppliers to Defendants, their employees, or any other entity managed or controlled in whole or in part by Defendants, without the necessity of identification or prior notice; and

C. Defendants shall permit representatives of the Commission to interview any employer, consultant, independent contractor, representative, agent, or employee who has agreed to such an interview, relating in any way to any conduct subject to this Order. The person interviewed may have counsel present.

Provided however, that nothing in this Order shall limit the Commission's lawful use of compulsory process, pursuant to Sections 9 and 20 of the FTC Act, 15 U.S.C. §§ 49, 57b-1, to obtain any documentary material, tangible things, testimony, or information relevant to unfair or deceptive acts or practices in or affecting commerce (within the meaning of 15 U.S.C. § 45(a)(1)).

IX.

COMPLIANCE REPORTING

IT IS FURTHER ORDERED that, in order that compliance with the provisions of this Order may be monitored:

A. For a period of three (3) years from the date of entry of this Order, Defendants shall notify the Commission in writing of any changes in the corporate structure of Defendants or any business entity that a Defendant directly or indirectly controls, or has an ownership interest in, that may affect compliance obligations arising under this Order, including, but not limited to: incorporation or other organization; a dissolution, assignment, sale, merger, or other action that would result in the emergence of a successor entity; the creation or dissolution of a subsidiary, parent, or affiliate that engages in any acts or practices subject to this Order; or a change in the business name or address, at least thirty (30) days prior to such change, *provided* that, with respect to any proposed change about which Defendants learn less that thirty (30) days prior to the date such action is to take place, the Commission shall be notified as soon as is practicable after obtaining such knowledge.

B. One hundred twenty (120) days after the date of entry of this Order and annually thereafter for a period of five (5) years, Defendants each shall provide a written report to the FTC, which is true and accurate and sworn to under penalty of perjury, setting forth in detail the

manner and form in which they have complied and are complying with this Order. This report shall include, but not be limited to:

1. A copy of each acknowledgment of receipt of this Order, obtained pursuant to the Section titled "Distribution of Order"; and

2. Any other changes required to be reported under Subsection A of this Section.

C. Defendants shall notify the Commission of the filing of a bankruptcy petition by any Defendant within fifteen (15) days of filing.

D. For the purposes of this Order, Defendants shall, unless otherwise directed by the Commission's authorized representatives, send by overnight courier all reports and notifications required by this Order to the Commission, to the following address:

Associate Director for Enforcement
Federal Trade Commission
600 Pennsylvania Avenue, N.W.
Washington, D.C. 20580
RE: *FTC v. Iovate Health Sciences USA, Inc.*, Civil Action No._____

Provided that, in lieu of overnight courier, Defendants may send such reports or notifications by first-class mail, but only if Defendants contemporaneously send an electronic version of such report or notification to the Commission at: DEBrief@ftc.gov.

E. For purposes of the compliance reporting and monitoring required by this Order, the Commission is authorized to communicate directly with Defendants.

X.

RECORD KEEPING PROVISIONS

IT IS FURTHER ORDERED that, for a period of six (6) years from the date of entry of this Order, Defendants and any business of which any Defendant is a majority owner or otherwise directly or indirectly manages or controls the business, and their agents, employees, officers, corporations, and those persons in active concert or participation with them who receive actual notice of this Order by personal service or otherwise, are hereby restrained and enjoined from failing to create and retain the following records:

A. Accounting records that reflect the cost of products covered by Sections I through III of this Order sold, revenues generated, and the disbursement of such revenues;

B. Personnel records accurately reflecting: the name, address, and telephone number of each person employed in any capacity by such business, including as an independent contractor; that person's job title or position; the date upon which the person commenced work; and the date and reason for the person's termination, if applicable;

C. Customer files containing the names, addresses, phone numbers, dollar amounts paid, quantity of products covered by Sections I through III of this Order purchased, and description of products covered by Sections I through III of this Order purchased;

D. Complaints and refund requests relating to products covered by Sections I through III of this Order (whether received directly, indirectly, or through any third party) and any responses to those complaints or requests;

E. Copies of all advertisements, promotional materials, sales scripts, training materials, websites, or other marketing materials utilized in the advertising, marketing,

promotion, offering for sale, sale, or distribution, of products covered by Sections I through III of this Order;

F. All materials that were relied upon in making any representations contained in the materials identified in Subparagraph 5 above, including all documents evidencing or referring to the accuracy of any claim therein or to the benefits, performance, or efficacy of any products covered by Sections I through III of this Order, including, but not limited to, all tests, reports, studies, demonstrations, or other evidence that confirms, contradicts, qualifies, or calls into question the accuracy of any claim regarding the benefits, performance, or efficacy of any products covered by Sections I through III of this Order, including complaints and other communications with consumers or with governmental or consumer protection agencies;

G. Records accurately reflecting the name, address, and telephone number of each manufacturer or laboratory engaged in the development or creation of any testing obtained for the purpose of manufacturing, labeling, advertising, marketing, promoting, offering for sale, selling, or distributing any products covered by Sections I through III of this Order;

H. Copies of all contracts concerning the manufacturing, labeling, advertising, marketing, promotion, offering for sale, sale, or distribution of any products covered by Sections I through III of this Order; and

I. All records and documents necessary to demonstrate full compliance with each provision of this Order, including, but not limited to, copies of acknowledgments of receipt of this Order required by the Sections titled "Distribution of Order" and "Acknowledgment of

Receipt of Order" and all reports submitted to the FTC pursuant to the Section titled "Compliance Reporting."

XI.

DISTRIBUTION OF ORDER

IT IS FURTHER ORDERED that, for a period of three (3) years from the date of entry of this Order, Defendants shall deliver copies of the Order as directed below:

A. Defendants shall deliver a copy of this Order to: (1) each of its principals, officers, directors, and managers; (2) all of its employees, agents, and representatives who engage in conduct related to the subject matter of the Order; and (3) any business entity resulting from any change in structure set forth in Subsection A of the Section titled "Compliance Reporting." For current personnel, delivery shall be within five (5) days of service of this Order upon Defendant. For new personnel, delivery shall occur prior to their assuming their responsibilities. For any business entity resulting from any change in structure set forth in Subsection A of the Section titled "Compliance Reporting," delivery shall be at least ten (10) days prior to the change in structure.

B. Defendants shall secure a signed and dated statement acknowledging receipt of the Order, within thirty (30) days of delivery, from all persons receiving a copy of the Order pursuant to this Section.

XII.

ACKNOWLEDGMENT OF RECEIPT OF ORDER

IT IS FURTHER ORDERED that Defendants, within five (5) business days of receipt of this Order as entered by the Court, shall submit to the Commission a truthful sworn statement acknowledging receipt of this Order.

XIII.

RETENTION OF JURISDICTION

IT IS FURTHER ORDERED that this Court shall retain jurisdiction of this matter for purposes of construction, modification, and enforcement of this Order.

SO ORDERED:

Dated: July 29, 2010

Richard J. Leeman
UNITED STATES DISTRICT JUDGE

SO STIPULATED AND AGREED:

FOR THE FEDERAL TRADE COMMISSION:

THEODORE H. HOPPOCK
DEVIN W. DOMOND
ELISE D. WHANG
SYDNEY KNIGHT
Federal Trade Commission
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EXHIBIT 2

Svetol®, green coffee extract, induces weight loss and increases the lean to fat mass ratio in volunteers with overweight problem

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° Ospedale SS. Antonio e Margherita, Dipartimento Medico-Ambulatorio Obesità, Tortona, Italy
• Berkem®, Le Marais ouest, BP 4, 24 680 Gardonne, France

ABSTRACT

In order to test the effects of Svetol®, a green coffee extract rich in chlorogenic acids with specific ratio between 5-caffeoylquinic acid and others caffeoylquinic acid isomers, on weight loss, 50 volunteers with body mass index superior to 25 were selected. They were randomized in two groups, control group (n = 20) receiving placebo, treated group (n = 30) receiving Svetol®. Each volunteer took one capsule of Svetol® or placebo twice a day with main meal, for 60 days. Changes in weight, body mass index (BMI), Muscle Mass/Fat Mass ratio (MM/FM) and self-evaluation of physical aspect were recorded at T0 and T60. After 60 days of treatment, a mean reduction in weight of 4.97 +/- 0.32 kg (5.7%) was observed in the Svetol® group compared to control group in which the mean reduction was 2.45 +/- 0.37 kg (2.9%) ($p < 0.001$). Consequently, body mass index decreased significantly in Svetol® group compared to control group. Moreover, MM/FM ratio was increased significantly in Svetol® group compared to control group: 4.1 +/- 0.7% *vs* 1.6 +/- 0.6 respectively ($p = 0.01$). The significant decrease of weight, boby mass index and fat mass showed that Svetol® is able to exacerbate effect of a bland low caloric diet in volunteers who have overweight. This effect could be explained by increasing the consumption of fatty deposits, as shown by change in the MM/FM ratio, and by preventing them from being accumulated.
To conclude, Svetol® could be used to aid the dietetics prescription in a useful and positive manner.

Key words: chlorogenic acids, Svetol®, weight, muscle mass/fat mass ratio

INTRODUCTION

Hydroxycinnamic acids are one of the major classes of phenolic compounds. They are present in a large variety of fruits and vegetables [1, 2]. The major representative of hydroxycinnamic acids in food is caffeic acid. It largely occurs conjugated with quinic acid as in chlorogenic acid (5-caffeoylquinic acid) **(Figure 1)**. Coffee, one of the most widely consumed beverages in the world, is the major dietary source of chlorogenic acids.
Chlorogenic acid has antioxidant properties showed by its ability to scavenge various free radicals when tested *in vitro* [3-5]. Moreover, chlorogenic acid reduces glucose uptake by favouring the dissipation of the Na^+ electrochemical gradient [6] and inhibits the activity of hepatic glucose-6-phosphatase which is implicated in glucose homeostasis [7, 8].
In vivo, when ingested under coffee form, chlorogenic acid increases the plasma antioxidant capacity [9]. Chlorogenic acid is also able to reverse the prooxidant effects of drugs such as paraquat [10] and have been reported to prevent different cancers and cardiovascular diseases in several experimental studies on animal models [11-15]. Therefore, we hypothesized that chlorogenic acid modulating glucose metabolism and decreasing oxidative stress could limit overweight, obesity development and secondary diseases

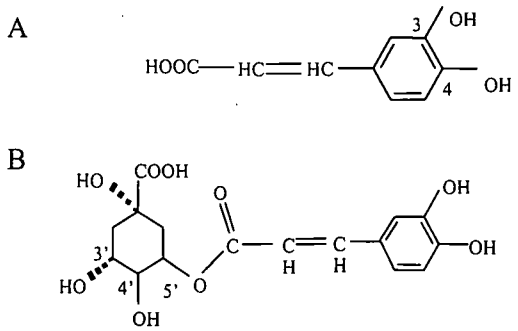

Figure 1: Chemical structure of caffeic (A) and chlorogenic acids (B)

associated with as type 2 diabetes mellitus or cardiovascular problems.

The aim of the present work was to evaluate if Svetol®, a green coffee extract, could decrease overweight in volunteers who had body mass index (BMI) superior to 25.

SUBJECTS AND METHODS

Chemicals

Svetol®, decaffeinated green coffee extract, were purchased from Berkem® SA (Gardonne, France).

Subjects

Fifty volunteers of both sexes, aged from 19 to 75, were assigned at random to the group of 30 in active treatment, and 20 in placebo treatment. The participants of both groups were homogeneous in weight and muscle mass/fat mass (MM/FM) ratio, characterized by an overweight problem, BMI superior to 25, and the acceptance of a bland low caloric diet. Exclusion criteria were as follows: acute or chronic gastro-intestinal pathologies; gastro-intestinal infections and/or parasitosis; severe hyper-tension (P.A. above 120 mm.); gastro-intestinal cancers; serious or chronic metabolic pathologies; big drinkers; assumption of products for the control of weight and glycaemia; a known intolerance to any of the components of the product under examination.

Svetol® supplementation

The product was prepared in jars of 30 capsules absolutely identical. Composition of the product (active capsules) under experimentation was given in **table 1.** Placebo capsules contained the same components as the active capsule, Svetol® was substituted by an identical quantity of maltodextrin (200 mg).

	mg/capsule
Svetol®	200
Starch	0.04
Magnesium stereate	0.015
Silica micronized	0.008
White gelatine	0.087

Table 1: Composition of the Svetol® capsule

Study design

Volunteers took one capsule with each main meal, twice a day, for 60 days. Every participant was given treatment sufficient for 30 days (two jars) when they began the study (T0) and the rest (two jars) at the T30 day.

Data collection and parameters of evaluation

In the course of the first check-up, the following data were gathered: age, height, sex, weight, BMI, MM/FM ratio, self-evaluation of physical aspect.
Changes in weight, BMI, MM/FM ratio, self-evaluation of physical aspect were recorded again at T60. An evaluation of compliance and verification of the presence of side effects was undertaken at T30 and T60.
MM/FM ratio was determined by Bioelectric Impedance Analysis. Self-evaluation of physical aspect was done by scale from 0 = very negative to 10 = excellent.

Evaluation of effectiveness, compliance and tolerability

At the end of treatment, effectiveness, compliance and tolerability were verified with regard to the end-points by comparing the changes in the data recorded at T60 to those at T0.
Therefore, changes of weight, BMI, MM/FM ratio, self-evaluation of physical aspect in the active group were compared to those recorded in the placebo group.
The effectiveness was based on those participants who completed the study. Compliance and tolerability were based on all participants.

Statistical analysis

Numerical values are mean +/- SEM (n = 20 for control group or 30 for treated group). Data were entered into Instat statistical analysis program (Instat, San Diego, CA). Student t-test (parametric test) or Mann-Whitney test (non-parametric test) determined the difference between values. Differences with $p \leq 0.05$ were considered significant.

RESULTS

Weight loss and Body Mass Index

After 60 days of treatment, a mean reduction in weight of 4.97 +/- 0.32 kg (-5.7 +/- 0.3%) was observed in the Svetol® group compared to control group in which the mean reduction was 2.45 +/- 0.37 kg (-2.9 +/- 0.4%). These means are significantly different ($p < 0.001$) **(Figure 2A)**. Consequently, body mass index decreased significantly in Svetol® group compared to control group (-1.9 +/- 0.1 kg/m^2 *vs* -0.9 +/- 0.1 kg/m^2 ; $p < 0.001$) **(Figure 2B)**.

Muscle Mass/ Fat Mass ratio

In Svetol® group, MM/FM ratio was increased significantly compared to control group: +4.1 +/- 0.7% *vs* +1.6 +/- 0.6 respectively ($p = 0.01$) **(Figure 3)**.

Self-evaluation of physical aspect

No significant difference about the appearance was observed between both groups at T60 (6.6 +/- 1.05 *vs* 6.5+/- 1.31 for placebo and Svetol® groups respectively) but both groups observed an amelioration of the physical appearance between T0 and T60 ($p < 0.05$ for each group).

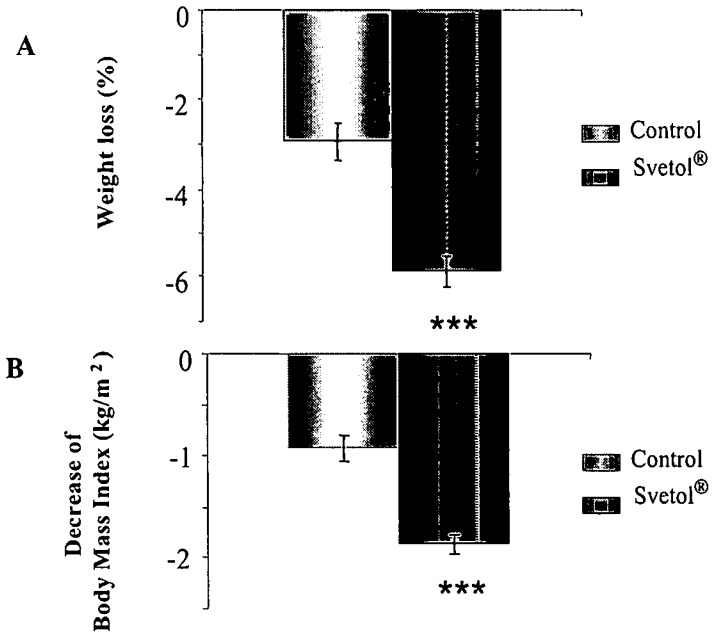

Figure 2: (A) Weight loss (%) and (B) decrease of BMI (kg/m^2) after 60 days treatment. Values are means +/- SEM, n = 20 for control group, n = 30 for Svetol® group. Means are significantly different (*, $p < 0.001$ vs. control group).

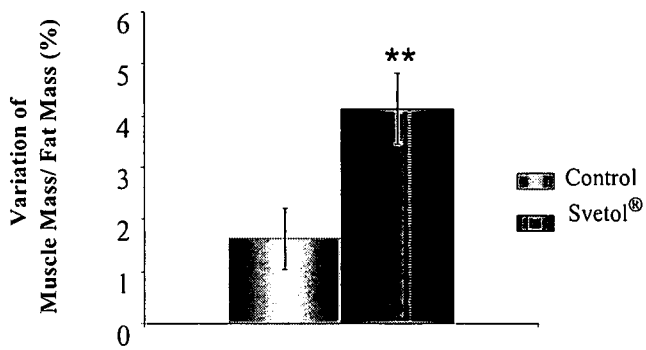

Figure 3: Variation of muscle Mass/ fat Mass ratio after 60 days of treatment (%). Values are means +/- SEM, n = 20 for control group, n = 30 for Svetol® group. Means are significantly different (**, $p = 0.01$ vs. control group).

DISCUSSION

Obesity is a serious public health problem [16]. Overweight and obesity are the cause of health problems of varying degrees of seriousness: asthenia, osteo-arthicular, psychological and cardio-vascular problems.

The reality is that this condition has a negative impact on the quality of life, and in the case of obesity, it can even lead to a reduction in life expectancy.

With the exception of serious neuro-endocrine pathologies the problem is caused mainly by lifestyle. A rational diet in quantity and quality, combined with some physical exercise can help to obtain some loss of weight. A change in lifestyle is not simple so in order to reach the desired goal of controlling weight pharmaceutical products are used as well as nutritional supplements with various compositions, fat burners, all with the aim of contrasting the lack of balance between the number of calories introduced and the number of those consumed which leads to overweight. There is a relationship between the amount of carbohydrates in the diet and the amount of fats in the adipose reserves since the carbohydrates are responsible for most of the calories introduced [17] and the intake of sugars reduces energy consumption. In normal production and activity of insulin, the calories introduced are burnt up without transforming the lipids into stock. On the other hand, if the amount of glucose present in the blood is in excess with regards to its use and to the hepatic glycogenesis, this excess glucose (owing to the insulin which has been increased by the hyperglycemia) enters into the adipocytes where it is stored as fat reserves [18]. The consequences are: (i) the fat reserves are not used to produce energy; (ii) an increase of adipocytes.

In diets the lower quantity of carbohydrates consumed is a way to "force" the organism to burn up the fat which has been deposited in the adipocytes and therefore to lose weight. It is possible to improve the effect of the lower amounts of carbohydrates consumed by exploiting the hepatic activity to regulate the glycemia level. When glucose level in the blood is lower than 1g/L, the liver synthesized glucose-6-phosphate (G6P) by an hexokinase, hydrolysed G6P by means of a glucose-6-phosphatase and released glucose into the bloodstream. It's glycogenolysis. If this sequence is interrupted the fatty deposits do not increase, but are instead used for the production of energy.

The aim of the present work was to evaluate if Svetol®, green coffee extract concentrated in chlorogenic acids with specific ratio between 5-caffeoylquinic acid and others caffeoylquinic acid isomers, could decrease overweight in volunteers by fat burning action as suggested by *in vitro* studies showing inhibition of the activity of hepatic glucose-6-phosphatase by 5-caffeoylquinic acid [7, 8].

The significant decrease of weight and fat mass showed that Svetol® is able to exacerbate effect of a bland low caloric diet in volunteers who had overweight. This effect could be explained by increasing the consumption of fatty deposits, as shown by change in the MM/FM ratio, and by preventing them from being accumulated.

From results presented here and bibliography, Svetol®'s mechanism could be proposed: first of all, associated with the diet, it inhibits glucose absorption in the small intestine[6]. In addition, by inhibiting the activity of glucose-6-phosphatase [7, 8], it limits the release of glucose into the general circulation [19, 20] and therefore limits

insulinemia. This mechanism engenders two results: (i) less fatty deposits in the adipose tissue and a more difficult access into the adipose cells owing to a reduction in insulin activity; (ii) consumption of fat reserves, where there is a lack of glucose, as a source of energy at the disposition of the organism and therefore, as in the previous case, a case of loss of weight.

However, mechanism proposed depends on bioavailability of chlorogenic acid. Recently, fate and metabolism of chlorogenic acid (5-caffeoylquinic acid) in the gastro-intestinal tract of rats were explored to determine the form under which this ester of caffeic acid is absorbed through the different parts of the gut barrier.

After analysis of the different gastro-intestinal contents, it appeared that chlorogenic acid is stable in the stomach and the small intestine but cleaved into caffeic acid in the caecum by the microflora [21]. Consequently, stability of chlorogenic acid in the small intestine is coherent with glucose absorption inhibition in this part of the gut. Moreover, whereas it was shown that chlorogenic acid was hydrolysed into enterocytes before secretion on the serosal side [22], it was absorbed under intact form from the stomach **[21]** and found in gastric vein and aorta without conjugation (glucuronidation, sulfation or methylation). This result suggests that chlorogenic acid is able to rejoin the liver without modification, which is in accordance with its activity of hepatic glucose-6-phosphatase inhibition.

Thus, chlorogenic acid bioavailability studies supported Svetol®'s mechanism proposed.

To conclude, Svetol® has demonstrated its validity and could be used to aid the dietetics prescription in a useful and positive manner.

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EXHIBIT 3

EXHIBIT 3

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Article

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Supplementation of a High-Fat Diet with Chlorogenic Acid Is Associated with Insulin Resistance and Hepatic Lipid Accumulation in Mice

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ABSTRACT: The increasing prevalence of the metabolic syndrome requires a greater need for therapeutic and prevention strategies. Higher coffee consumption is consistently associated with a lower risk of type 2 diabetes in population studies. Dietary polyphenols have been linked to benefits on several features of the metabolic syndrome. Chlorogenic acid (CGA), a major component of coffee, is one of the most consumed polyphenols in the diet. In our study, we conducted a controlled dietary intervention over 12 weeks in male mice. There were three dietary groups: (i) normal diet, (ii) high-fat diet, and (iii) high-fat diet + CGA. We assessed the effect of CGA at a physiologically obtainable dose (1 g/kg of diet) on high-fat-diet-induced obesity, glucose intolerance, insulin resistance, and also fatty acid oxidation and insulin signaling in C57BL/6 male mice. Supplementation of CGA in the high-fat diet did not reduce body weight compared to mice fed the high-fat diet alone ($p = 0.32$). CGA resulted in increased insulin resistance compared to mice fed a high-fat diet only ($p < 0.05$). CGA resulted in decreased phosphorylation of AMP-activated protein kinase (AMPK) ($p < 0.001$) and acetyl carboxylase β (ACCβ), a downstream target of AMPK ($p < 0.05$), in liver. The liver of mice fed a high-fat diet supplemented with CGA had a higher lipid content ($p < 0.05$) and more steatosis relative to mice fed a high-fat diet only, indicating impaired fatty acid oxidation. This study suggests that CGA supplementation in a high-fat diet does not protect against features of the metabolic syndrome in diet-induced obese mice.

KEYWORDS: *Chlorogenic acid, glucose tolerance, insulin sensitivity, fatty acid oxidation, mouse, metabolic syndrome*

INTRODUCTION

The metabolic syndrome consists of a group of metabolic abnormalities, such as abdominal obesity, dyslipidemia, hyperglycemia, and hypertension.[1] The condition is associated with the increased risk of developing cardiovascular disease and type 2 diabetes.[1,2] Emergence of metabolic syndrome incidence has resulted in an increased need for therapeutic and prevention strategies. Lifestyle changes[3] and potential treatment that targets specific molecules for regulation of metabolic pathways[4] are recommended approaches toward managing metabolic syndrome.

Epidemiological studies have shown inverse associations between coffee consumption and risk of developing chronic diseases, such as type 2 diabetes mellitus[5] and cancer.[6] These potential benefits are also indicated in individuals consuming decaffeinated coffee.[5,7] This suggests that compounds in coffee other than caffeine may be responsible for the health benefits.

Numerous studies suggest health benefits of polyphenols. They include reducing blood pressure,[8] improvement of endothelial function and nitric oxide status,[9] and augmentation of insulin sensitivity.[10] Chlorogenic acid (CGA), is an ester of caffeic acid and quinic acid.[11] This compound is rich in coffee, as well as other sources, such as in fruits like plums,[12] apples, and berries.[13] Coffee consumers can obtain up to 1 g of CGA from daily consumption.[11] In a coffee-drinking population, CGA is likely to be one of the major polyphenols in the diet.[14] Coffee polyphenols have been shown to have various health-protective effects, such as suppressing body fat accumulation,[15] reducing liver damage,[16] and inhibiting hyperglycaemia, hyperinsulinemia, and hyperlipidemia.[17] However, these studies either looked at coffee polyphenols, which includes a combination of many phenolic acids, including CGA and ferulic acid,[15] or coffee extract, which may have been a combined effect from the various compounds found in coffee. A recent study that looked at specific coffee polyphenols has reported that caffeic acid stimulates AMP-activated protein kinase (AMPK) activity in rat skeletal muscle and enhances insulin-independent glucose transport, while none of the effects were seen with CGA treatment.[18] However, effects of pure

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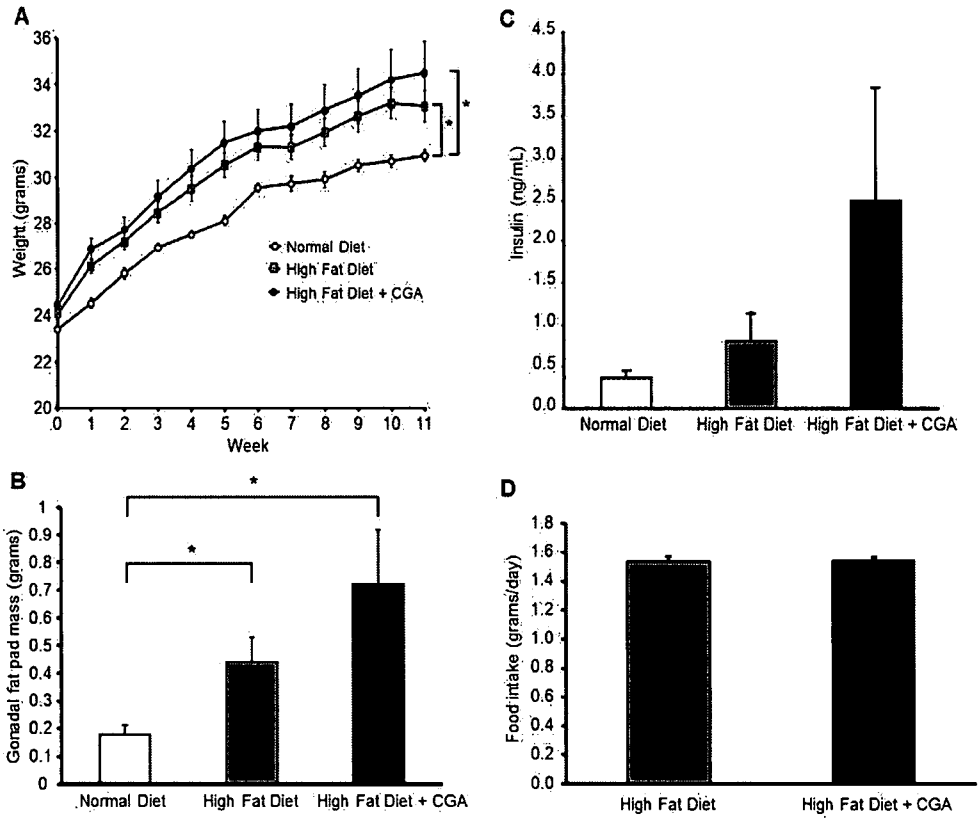

Figure 1. High-fat-diet-induced weight gain with CGA supplementation. (A) Weight gain in mice fed a normal diet (white circle), high-fat diet (gray square), and high-fat diet + CGA (black circle), (B) gonadal fat pad weights, (C) fasting insulin measurements at week 12, and (D) food intake. Data are expressed as the mean ± SEM; n = 10 mice per group for A and D and n = 5 for B and C. (*) $p < 0.05$.

CGA, which is the most abundant form of phenolic acid in coffee, on risks of metabolic disorders remain to be fully elucidated.

The aim of the present study was to test the effect of CGA on high-fat-diet-induced obesity, glucose intolerance, and insulin resistance in mice. We also assessed the effects of CGA on fatty acid oxidation and insulin signaling.

■ MATERIALS AND METHODS

Experimental Animal and Diets. Male C57BL/6 mice were obtained from the Animal Resources Centre, Murdoch, Western Australia, Australia, and were maintained on a normal diet (14.3 MJ/kg, 76% of energy from carbohydrate, 5% from fat, and 19% from protein; Specialty Feeds, Glen Forrest, Western Australia, Australia) until 7 weeks of age. The mice were allowed to acclimatize to conditions in the animal holding room, and they were maintained on a 12 h light/dark cycle. Mice were then switched to 3 groups of different diets (n = 10 in each group, 5 mice/cage), which are a normal diet, a high-fat diet (19 MJ/kg, 36% of energy from carbohydrate, 43% of energy from fat, and 21% from protein; Specialty Feeds), and a high-fat diet that contained 1 g of CGA/kg of diet (Atlantic SciTech Group, Linden, NJ) for a further 12 weeks. Water and feed were available to the animals *ad libitum*. All surgery was performed under methoxyflurane anesthesia, and all efforts were made to minimize suffering.

Ethics Statement. All animal experiments were approved by the Royal Perth Hospital Animal Ethics Committee (approval number RS10/11-12).

Body Weight, Adiposity, and Basal Insulin Measurement. Body weights of mice were measured weekly throughout the study. Gonadal fat pad mass was also measured at the time of sacrifice. Mice were fasted for 5 h prior to sacrifice. Fasting blood samples were collected via cardiac puncture, and serum was obtained. From this sample, insulin was measured using standard enzyme-linked immunosorbent assay (ELISA) kits as previously described.[19]

Metabolic Assays. Glucose tolerance tests (GTTs) were performed at weeks 5 and 10 of the experiment, while insulin tolerance tests (ITTs) were performed at weeks 6 and 11 of the experiment. Food was withdrawn from mice 5 h prior to testing. Blood samples were obtained by tail bleeding, and glucose levels were measured using a glucometer (AccuCheck II; Roche, Castle Hill, New South Wales, Australia) immediately before and at 15, 30, 45, 60, 90, and 120 min after an intraperitoneal injection of glucose (1 g/kg of body mass) or insulin (0.5 unit/kg of body mass).

Food Intake. Food was weighed manually for mice fed either a high-fat diet only or a high-fat diet with CGA supplementation for 11 weeks. The grams of diet consumed per mouse were then determined per day.

Acute Insulin Signaling Experiment. For insulin signaling experiments, mice were anaesthetized with methoxyflurane before an intraperitoneal injection with insulin (2 units/kg) or saline. Subsequently, liver, adipose tissue, and skeletal muscle samples were obtained within 5 min of injection and snap-frozen in liquid nitrogen, before being analyzed for protein concentration.

Liver and Adipose Tissue Histology. At the end of the experiment, white adipose tissue and liver were dissected and fixed in 4% paraformaldehyde (w/w) overnight before being incubated in 50% ethanol (v/v) and then promptly embedded with paraffin. The tissues were then cut into 4 μm sections and stained with hematoxylin and eosin, before being mounted using DePeX (Sigma-Aldrich, St. Louis, MO). Sections were then visualized and photographed using the Olympus 1X71 microscope (Olympus, Mt. Waverly, Victoria, Australia).

Hepatic Lipid Analysis. Total lipid from the liver was extracted with a chloroform–methanol mixture (2:1) according to the method by Folch et al.[20] Empty glass tubes were weighed prior to the

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extraction process. After completing the extraction process, extracts were dried under vacuum using a sample concentrator (miVac, Ipswich, U.K.) and then the tubes were reweighed to determine the weight of lipid extracted from the liver samples.

Western Blot Analysis of Proteins Associated with Fatty Acid Oxidation and Insulin Signaling. Liver, white adipose tissue, and skeletal muscle (quadricep) were dissected from mice on the final day of the experiment and were snap-frozen in liquid nitrogen. Tissue samples were lysed by homogenization in cytostolic extraction buffer containing protease and phosphatase inhibitors. The lysates were then centrifuged at 15493*g* for 10 min at 4 °C; supernatants were collected; and the protein concentration was determined using BCA Protein Assay Reagent (bicinchoninic acid; Thermo Scientific, Hanover Park, IL). Samples were then separated with sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE), and western blotting was carried out to detect total AKT, phosphorylated AKT (Ser^{473}), phosphorylated acetyl carboxylase β (ACCβ Ser^{79}), and phosphorylated AMP-activated protein kinase (AMPK Thr^{172}) using primary antibodies from Cell Signaling Technology (Danvers, MA).[21,22] The β-actin antibody was obtained from AbCam. Horseradish-peroxidase-conjugated secondary antibodies were used, and protein bands were detected by chemi-illuminescence using the Multi Image II (Alpha Innotech).

Statistical Analyses. Statistical analyses were performed using IBM SPSS Statistics 19 (IBM Corporation, Armonk, NY) and SAS 9.3 (SAS Institute, Inc., Cary, NC). Results are expressed as the mean ± standard error of the mean (SEM). Mean values were compared for differences by analysis of variance with Tukey's adjustment for multiple comparisons (three-group analyses) or Student's *t* test for unpaired samples (two-group analyses). $p < 0.05$ was considered to be statistically significant. For data with repeated measures over time (weight, GTT, and ITT), random-effect linear models were fitted in SAS using the PROC MIXED command to observed data for each variable (weight and glucose). The mouse number was included as a random factor in all models. The models also contained fixed effects for treatment group (diet) and time as a categorical variable.

RESULTS

Effect of CGA Supplementation on High-Fat-Diet-Induced Obesity and Insulin Levels in C57BL/6 Mice. The high-fat diet and high-fat diet + CGA groups both displayed a higher rate and absolute body weight increase compared to the normal diet group (Figure 1A). The rate and absolute body weight increase did not differ between the two high-fat diet groups. Mice fed the high-fat diet or high-fat diet + CGA also displayed increased gonadal fat pad mass (Figure 1B) compared to the mice fed the normal diet. Differences in gonadal fat pad mass between the two high-fat diet groups were not significant ($p = 0.23$). Both body weight and gonadal fat pad measurements confirmed that the high-fat diet induced obesity in C57BL/6 mice.

We measured fasting insulin levels in basal serum of mice using ELISA. A trend for hyperinsulinemia was evident in the high-fat diet + CGA fed mice (Figure 1C) compared to high-fat diet fed mice and normal diet fed mice. All subsequent analysis presented in this paper will now compare high-fat diet fed mice to the high-fat diet fed mice supplemented with CGA.

We also measured the estimate of food intake in both high-fat diet fed mice and high-fat diet + CGA fed mice (Figure 1D). Food intake was similar between the two groups of mice.

CGA Supplementation Promoted Glucose Intolerance and Insulin Resistance. We performed intraperitoneal GTT (at weeks 5 and 10) and ITT (at weeks 6 and 11) after commencement of feeding (panels A and B of Figure 2 and panels A and B of Figure 3). A tendency for glucose intolerance was observed with CGA supplementation compared to the high-fat diet alone, particularly at week 10 (Figure 2B). Interestingly, we demonstrated that the CGA supplementation group was markedly more insulin-resistant compared to the high-fat diet alone mice ($p < 0.05$), and this increased with the duration of the diet (panels A and B of Figure 3). We conducted systematic analysis of insulin stimulation in a number of metabolic tissues to assess in which compartment insulin resistance was prevailing with CGA supplementation.

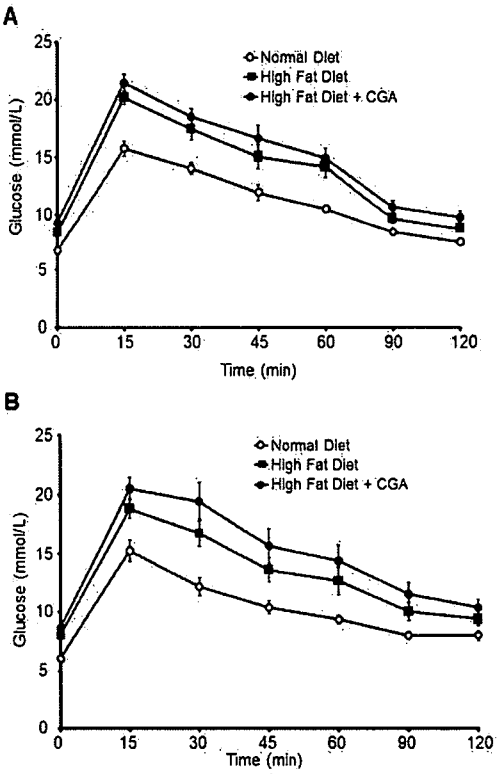

Figure 2. CGA supplementation induced a tendency for glucose intolerance in mice. GTT at (A) week 5 and (B) week 10 in normal diet (white circle), high-fat diet (gray square), and high-fat diet + CGA (black circle) fed mice. Data are expressed as the mean ± SEM; n = 9–10 mice per group.

CGA Resulted in Mild Insulin Resistance in White Adipose Tissue. Western blot analysis of insulin signaling in white adipose tissue confirmed reduced phosphorylation of Akt (Ser^{473}) with CGA supplementation (Figure 4A). High-fat diet fed mice showed a 10.8-fold increase in insulin-induced AKT phosphorylation compared to the CGA supplemented group, which had a 6.9-fold increase in insulin-induced AKT phosphorylation. However, the difference was not significant.

When assessing insulin stimulation in liver, we did not observe an effect as a result of CGA supplementation. This suggests that CGA-induced insulin resistance is not occurring in the liver (Figure 4B). Both groups of mice showed a 1.8-fold increase in insulin-induced AKT phosphorylation. We also assessed insulin-induced AKT phosphorylation in skeletal muscle (quadricep) (Figure 4C). From this analysis, we found no effect of CGA supplementation on insulin signaling in the skeletal muscle (quadricep), where the high-fat diet showed a 4.4-fold increase in insulin-induced AKT phosphorylation, while the CGA supplemented group displayed a 5.5-fold increase in insulin-induced AKT phosphorylation. This suggests that CGA-induced insulin resistance did not occur in the quadricep.

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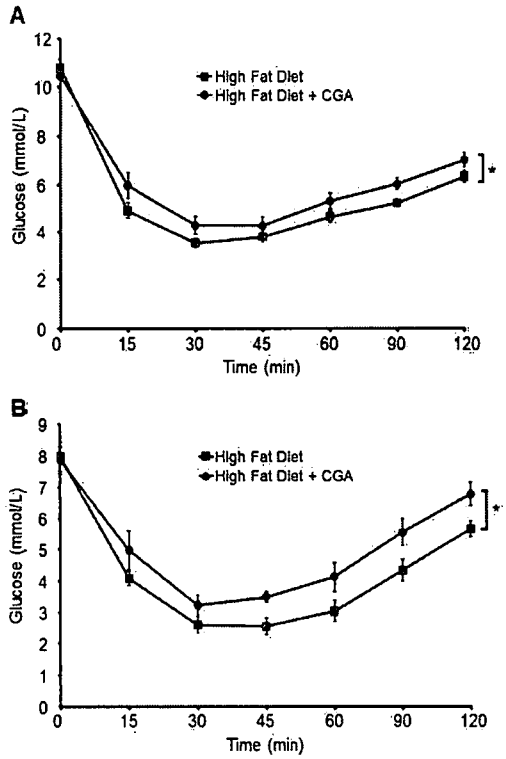

Figure 3. CGA supplementation induced insulin resistance in mice. ITT at (A) week 6 and (B) week 11 in high-fat diet (gray square) and high-fat diet + CGA (black circle) fed mice. Data are expressed as the mean ± SEM; n = 9−10 per group. (*) $p < 0.05$.

CGA Supplementation Reduced Fatty Acid Oxidation Signaling in Liver and White Adipose Tissue. We examined the phosphorylation of AMPK and ACCβ as markers of fatty acid oxidation in a number of metabolic tissues. Analysis of liver highlighted that phosphorylation of AMPK and its downstream target ACCβ was decreased in liver with CGA supplementation (Figure 5). This result suggests that decreased fatty acid oxidation prevailed in the mice after CGA supplementation. We examined liver histology using hematoxylin and eosin staining. Interestingly, we observed markedly more steatosis in the liver of high-fat fed mice supplemented with CGA (Figure 6B) compared to high-fat fed only mice (Figure 6A). Moreover, the hepatic lipid content was higher in mice supplemented with CGA compared to mice fed a high-fat diet alone (Figure 6C). This is consistent with the reduced phosphorylation of AMPK and ACCβ seen in the same group of mice, which suggests an impaired fatty acid oxidation pathway.

Fatty acid oxidation signaling was also assessed in white adipose tissue. In this tissue, CGA supplementation resulted in a tendency for decreased phosphorylation of ACCβ, the downstream target of AMPK, which suggests decreased fatty acid oxidation in white adipose tissue of mice fed a high-fat diet supplemented with CGA (Figure 7). Finally, assessment of white adipose tissue by hematoxylin and eosin staining revealed adipocyte hypertrophy in mice fed a high-fat diet supplemented with CGA compared to mice fed a high-fat diet alone (Figure 8).

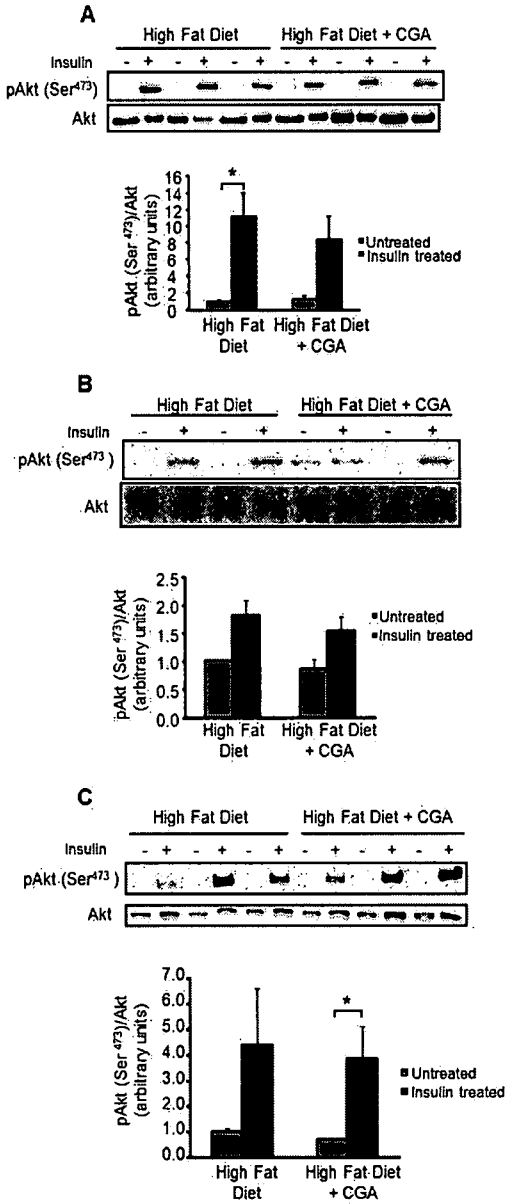

Figure 4. Effect of CGA supplementation on insulin sensitivity in white adipose tissue, liver, and skeletal muscle. Representative immunoblots of total and phosphorylated (Ser^{473}) Akt and quantification of insulin-stimulated phosphorylation of Akt (Ser^{473}) in (A) white adipose tissue, (B) liver, and (C) skeletal muscle. Data are expressed as the mean ± SEM; n = 4 mice per group. (*) $p < 0.05$.

■ DISCUSSION

We sought to assess the effect of CGA supplementation on diet-induced obesity, glucose intolerance, insulin resistance, and signaling pathways associated with glucose homeostasis and fatty acid oxidation in mice. Our results do not support the hypothesis that CGA can prevent development of features of the metabolic syndrome.

We demonstrated that 12 weeks of high-fat feeding induced an increase in body weight and hyperinsulinemia in C57BL/6J mice. The same observation has previously been seen by our group[23] and others.[24,25] Interestingly, a high-fat diet supplemented with CGA increased body weight gain compared to mice fed a normal diet. Mice fed a high-fat diet only and a high-

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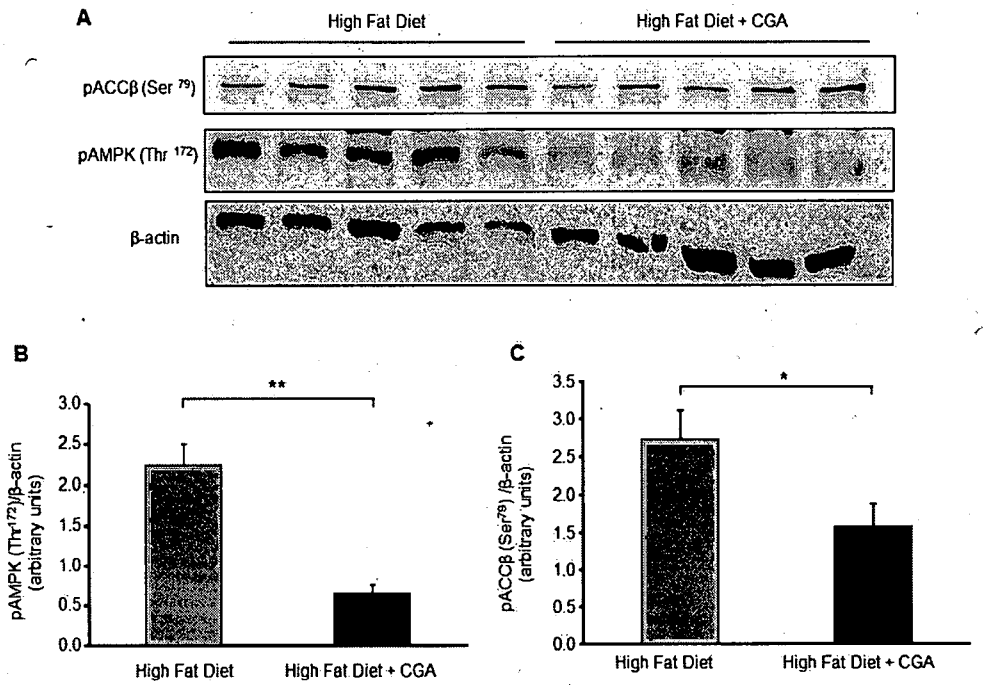

Figure 5. CGA supplementation decreases AMPK signaling in the liver. (A) Representative immunoblots and quantification of phosphorylation of (B) AMPK (Thr^{172}) and (C) ACCβ (Ser^{79}) in liver. Data are expressed as the mean ± SEM; n = 5 mice per group. (*) $p < 0.05$ and (**) $p < 0.001$.

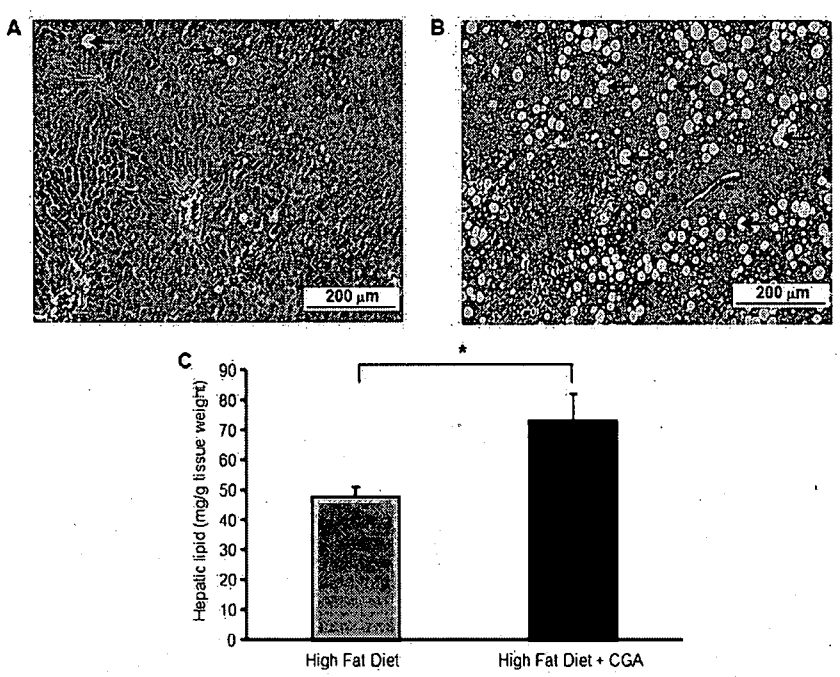

Figure 6. Effect of CGA supplementation on high-fat-diet-induced steatosis and lipid content in liver. Representative hematoxylin and eosin staining of liver of mice fed a (A) high-fat diet and (B) high-fat diet + CGA and (C) lipid quantitation. Arrows indicate steatosis. Data are expressed as the mean ± SEM; n = 10 per group. (*) $p < 0.05$.

fat diet with CGA supplementation showed similar body weights. Despite the similar body weight, fasting insulin was further elevated in mice fed a high-fat diet supplemented with CGA compared to mice fed a high-fat diet alone. Gonadal fat pad mass was also increased 2.5-fold in mice fed a high-fat diet compared to those fed a normal diet and was 4-fold higher in mice fed a high-fat diet supplemented with CGA when compared to those fed a normal diet. These results are not consistent with the study by Cho et al.,[26] who observed that CGA and its metabolite, caffeic acid, reduced weight gain and visceral fat mass in high-fat-diet-induced obese imprinting control region (ICR) mice. A recent study by Murase et al.[17] observed that coffee polyphenols suppressed body fat accumulation in high-fat-diet-induced obese mice.[17] It should be noted that our study used a higher dose of CGA (1 g/kg of diet) compared to the study by Cho et al.[26] (0.2 g/kg of diet).

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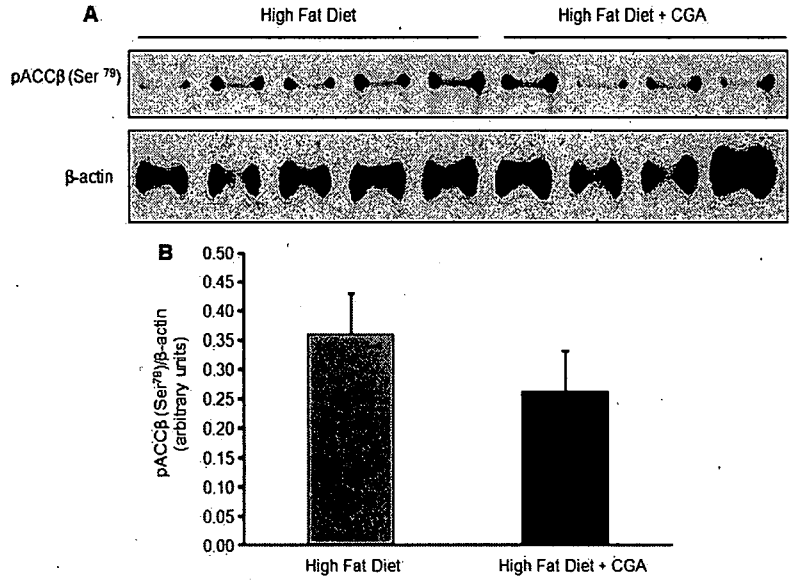

Figure 7. CGA supplementation reduces phosphorylation of ACCβ in white adipose tissue. (A) Representative immunoblots and (B) quantification of phosphorylation of ACCβ (Ser^{79}) in white adipose tissue. Data are expressed as the mean ± SEM; n = 4–5 mice per group.

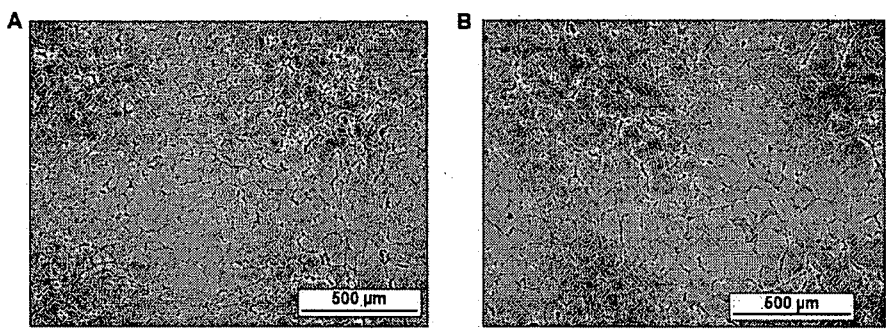

Figure 8. CGA supplementation promotes adipocyte hypertrophy. Representative hematoxylin and eosin staining of white adipose tissue of mice fed a (A) high-fat diet and (B) high-fat diet + CGA.

Cho et al.[26] employed a different strain of mice in their study. These differences could explain some of the variation in results compared to our study.

We also measured food intake in the mice fed either a high-fat diet only or a high-fat diet with CGA supplementation. Our results showed that there was no difference in food intake between the two groups (Figure 1D). Unfortunately, we did not collect feces in our current studies. Future studies should collect feces from mice fed either a high-fat diet only or a high-fat diet with CGA supplementation to compare the microbiota between the two groups of mice. These data may support a role for bacterial pathogens in the phenotypical differences observed between mice fed either a high-fat diet only or a high-fat diet with CGA supplementation. These future studies are vital because the CGA in the diet will be degraded by the action of the local microbiota to give rise to small bioactive phenolic acid and aromatic catabolites in the circulation.[27] Colonic metabolites of CGAs include *m*-coumaric acid, dihydroferulic acid, dihydrocaffeic acid, and feruloylglycine. These metabolites may be responsible for the observed phenotype, or they may work in concert.

Our study is not the first to demonstrate that higher doses of a particular compound or chemical may promote detrimental effects on health. A long-term French study demonstrated that moderate wine drinkers (<60 g of alcohol/day) had lower risks of deaths from all causes at all levels of systolic blood pressure. In this same study, there was no significant reduction in all-cause mortality in heavier drinkers.[28]

When determining the dose of a compound to administer to mice, it is vital to ensure that it will ultimately equate to physiological concentrations in humans. It has been highlighted that it would be naive to just use body weight to extrapolate safe doses from animals to humans. It has been suggested that using body surface area would allow for better estimates because the allometric scaling factor at least approximates that of clearance.[29] On the basis of body surface area, the dose in humans should be 405 greater than the dose in mice. Hence, in our current study, a single mouse would consume approximately 3 mg of CGA/day. On the basis of body surface area, this equates to 1215 mg of CGA in humans/day. This is a physiological dose in humans because a single cup of coffee contains approximately 250 mg of CGA (1215 mg of CGA = 5 cups of coffee).

To our knowledge, this is the first study of the effect of CGA on glucose tolerance and insulin sensitivity in high-fat-diet-induced obese mice. We did not observe any improvement in glucose tolerance in mice fed a high-fat diet supplemented with CGA. This is not in accordance with the study by Bassoli et al.,[30] who observed a reduced plasma glucose peak in the oral GTT following an acute oral administration of CGA at 3.5 mg/

kg of body weight in rats. Ong et al.[31] also found a reduction of the blood glucose level after intraperitoneal administration of 250 mg/kg of CGA in *db/db* mice. The different methods of CGA administration and dose used in the experiment may explain some of the variations in results compared to our study. We believe that performing the GTT and ITT on mice fed a high-fat diet supplemented with CGA is a more robust approach to reflect a natural consumption effect of this compound rather than administrating it through intraperitoneal injection or oral gavage. From the ITT, we observed a significant increase in insulin resistance in mice fed a high-fat diet supplemented with CGA. We also assessed insulin stimulation in metabolic tissues by measuring the phosphorylation of Akt (Ser^{473}). Phosphorylation of Akt because of insulin stimulation is required for insulin-stimulated glucose uptake and anabolic metabolism.[32] Therefore, an increased rate of Akt (Ser^{473}) phosphorylation reflects insulin sensitivity in the tissue. We saw a tendency for reduced insulin-stimulated phosphorylation of Akt in the white adipose tissue of mice fed a high-fat diet supplemented with CGA, which reflects a mild insulin resistance. This result does not correspond to some *in vitro* studies showing improvement of insulin signaling in 3T3-L1 adipocytes by chicory salad leaf extract containing CGA.[33] However, our result supports the increased insulin resistance observed from the ITT. We did not observe an effect of CGA supplementation on insulin sensitivity in the liver and quadricep muscle, suggesting that insulin resistance did not occur in these tissues.

We also assessed effects of CGA supplementation on signaling pathways associated with fat oxidation in the liver, white adipose tissue, and skeletal muscle. We and others have highlighted that phosphorylation of ACCβ at its critical site (Ser^{79})[34] by AMPK leads to the decrease in activity of ACCβ, resulting in reduced malonyl-CoA production, which, in turn, relieves inhibition of carnitine palmitoyl transferase 1 (CPT-1) and increases fatty acid oxidation.[35] In our study, we saw a markedly reduced phosphorylation of AMPK (Thr^{172}) and its downstream target ACCβ (Ser^{79}) in the liver, suggesting that reduced fatty acid oxidation is occurring in this tissue. Haematoxylin and eosin staining of the liver tissue sections showed that CGA supplementation in the high-fat diet resulted in increased steatosis in the liver, which supports the impaired fatty acid oxidation signaling in this tissue. The CGA supplementation was also found to increase the lipid content in the liver by 1.5-fold when compared to the liver of mice fed a high-fat diet alone. Our data are not in agreement with the study by Ong et al.,[31] which found that CGA increases phosphorylation of AMPK and ACCβ in L6 myotubes after incubation with CGA *in vitro*. However, results from *in vitro* studies may differ from those found *in vivo*. In white adipose tissue, there was a tendency for reduced phosphorylation of ACCβ in mice fed a high-fat diet supplemented with CGA compared to mice fed a high-fat diet only, suggesting decreased fatty acid oxidation. Haematoxylin and eosin staining of the white adipose tissue sections revealed that CGA resulted in adipocyte hypertrophy in mice. This supports that the data showed a tendency for impaired fatty acid oxidation pathways in white adipose tissue. The result from our study is not in accordance with data shown in the study by Cho et al.,[26] where they demonstrated that CGA reduced obesity and improved lipid metabolism in obese ICR mice. However, the lower dose of CGA used may explain some of the variation in results compared to our study. We also assessed phosphorylation of AMPK and ACCβ in quadricep. However, we did not observe an effect of CGA on this tissue. Tsuda et al.[18] also did not find an effect of CGA on phosphorylation of these proteins in epitrochlearis muscle but observed that caffeic acid, a metabolite of CGA, induced the phosphorylation of AMPK and ACCβ.

Our study does not support the hypothesis that supplementation of CGA to a high-fat diet will protect against features of the metabolic syndrome in obese mice. Further work especially on human intervention studies is required to determine if coffee polyphenols are able to protect against metabolic syndrome and type 2 diabetes in humans.

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Notes

The authors declare no competing financial interest.

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EXHIBIT 4

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Topical Review Article

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Green Coffee for Pharmacological Weight Loss

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Abstract

This review article evaluates if clinical data support the use of green coffee for weight loss. A literature search was conducted that yielded 5 clinical trials and 1 meta-analysis. Studies were evaluated for quality in accordance to clinical practice and US Food and Drug Administration guidelines. The amount of weight loss ranged from approximately 1 to 8 kg, with the meta-analysis finding a statistically significant difference in body weight, with a mean difference of −2.47 kg between green coffee and placebo (95% confidence interval = −4.23 to −0.72). The duration of trials varied between 4 and 12 weeks, and the dose of chlorogenic acid varied from 81 to 400 mg. Few published studies were in compliance with the US Food and Drug Administration guidelines. Despite the potentially clinically significant weight loss achieved in some published studies, all held significant limitations. Green coffee extract is not recommended as a safe or effective treatment for weight loss.

Keywords

green coffee, weight loss, obesity, chlorogenic acid

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Introduction

More than one third of the United States is considered obese, according to the Centers for Disease Control.[1] Obesity is known to contribute to comorbid conditions such as diabetes, hypertension, dyslipidemia, respiratory problems, and many other diseases, all of which may become life threatening. Patients are classified as obese if their body mass index is greater than or equal to 30 kg/m^2 and overweight if their body mass index is between 25 and 29.9 kg/m^2.[2] Since 1960, there has been a dramatic increase in the portion of the population classified as overweight or obese.[3]

The Federal Trade Commission has stated that at any given time, 70 million Americans are seeking weight loss, and in 2000, $35 billion was spent on dietary supplements with the intent of promoting weight loss.[4] With companies advertising weight loss supplements, with many claims being false or misleading, the Federal Trade Commission warns of potential risk to patients, as this may take the place of education patients could be receiving from health care professionals. In a comparison from 1992 to 2001, the amount of false or misleading advertisements related to weight loss supplements has dramatically increased. The US Food and Drug Administration has also questioned claims that dietary supplements cause significant weight loss.[5]

In 2007, US Food and Drug Administration created the "Guidance for Industry: Developing Products for Weight Management."[6] It is recommended that Phase III clinical trials assessing the efficacy and safety of medications for the use of weight loss are randomized, double-blind, and placebo-controlled. To assess the safety of the medications, it is recommended that at least 3000 subjects be given the active medication while at least 1500 subjects receive placebo, both for at least 12 months. It is also recommended that a lifestyle modification program be implemented into the trial. Primary endpoints should assess the amount of weight loss and the proportion of patients losing 5% of baseline body weight compared to placebo. It is expected that an efficacious agent would result in a mean weight reduction of 5% over 6 months. Secondary endpoints should look at metabolic parameters, such as blood pressure, pulse, lipids, glucose levels, hemoglobin A1C, and waist circumference.

Parameters suggested by the US Food and Drug Administration correlate with published obesity treatment guidelines.[3] Guidelines for initial management recommend implementing lifestyle modifications such as diet modification, exercise, and behavioral changes. If lifestyle modifications are not

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Table 1. US Food and Drug Administration–Approved Medications for Weight Loss.[7]

	Over the Counter	Prescription
Orlistat (Alli, Xenical)	X	X
Phentermine (Adipex)		X
Diethylpropion (Tenuate)		X
Phentermine/Topiramate (Qsymia)		X
Lorcaserin (Belviq)		X

successful, pharmacotherapy is an option. If severely obese, bariatric surgery can be considered if other options have failed.[3] Guidelines only recommend weight loss drugs when used in combination with diet and exercise for patients with a body mass index greater than or equal to 30 kg/m^2 with no obesity-related comorbidities (eg, diabetes mellitus, cardiovascular disease) or for those with body mass index greater than or equal to 27 kg/m^2 if the patient has obesity-related diseases. The US Food and Drug Administration approved prescription and nonprescription medications for obesity are listed in Table 1.

Currently, green coffee is being marketed for "natural" weight loss as a drink and in various solid oral dosage forms. This product has gained national interest and has appeared in the lay media, including *The Dr. Oz Show*.[8] In the weeks following a segment featuring green coffee on *The Dr. Oz Show*, with claims that it can help women lose 2 pounds per week based an in-house study, it was among the most popular Internet searches.[9]

Green coffee, classified as a dietary supplement, refers to raw, nonroasted coffee.[10] Chlorogenic acids, natural antioxidants present in large amounts in green coffee, are the active ingredients in green coffee thought to promote weight loss. Chlorogenic acid is present, to some extent, in roasted coffee, although much of it is destroyed in the roasting process. The most common chlorogenic acids are 5-O-caffeoylquinic acid, 2-O-caffeoylquinic acid, and 4-O-caffeoylquinic acid. Studies have been conducted to assess chlorogenic acid bioavailability and have shown that they are highly absorbed and metabolized when present in coffee.[11] The mechanisms of action of the chlorogenic acids, which are present in green coffee, include modulating glucose metabolism, lowering postprandial glucose, reducing glucose absorption through the intestines, and inhibiting fat accumulation. While caffeine may also promote weight loss, green coffee has a measured caffeine content similar to regular brewed coffee.[12] Studies suggest that chlorogenic acids, along with caffeine consumption, may impair glucose absorption rates.[13] According to the Natural Medicine Comprehensive Database, green coffee is considered "possibly safe" if used orally and appropriately.[12] Although little safety information exists regarding green coffee specifically, potential adverse drug events of green coffee include those related to high doses of caffeine, such as agitation, anxiety, arrhythmia, diuresis, headache, insomnia, and vomiting. Excessive caffeine exposure may also result in catecholamine release leading to acid/base, serum glucose, and serum potassium changes that could have serious cardiac implications.

Due to the wide availability of products containing green coffee and increasing popularity due to media exposure, it is expected that pharmacists and other health care professionals will encounter patient questions regarding these products. The objective of this review was to determine if clinical data support the use of green coffee for the purpose of weight loss.

Data Sources, Selection, and Extraction

A literature search using PubMed (1966 to November 2012) and International Pharmaceutical Abstracts (1976 to November 2012) was conducted using the terms green coffee, chlorogenic acid, and weight loss. The search was limited to English language articles. References of results were reviewed for additional relevant articles. Clinical trials, meta-analyses, or case reports involving the use of green coffee in humans were included in the review. The search identified 5 clinical trials and 1 meta-analysis, all of which are reviewed in the following section. Studies were assessed for accordance with US Food and Drug Administration guidance for weight loss trials.

Data Synthesis

In a prospective crossover trial, 16 subjects aged 22 to 46 were randomized to receive GCA, a commercial product containing green coffee extract, orally in a high dose of 350 mg 3 times daily, a low dose of 250 mg 2 times daily, and placebo 3 times daily.[14] Patients received each of these treatments for 6 weeks with a 2-week washout period in between treatments. The total duration of the trial was 22 weeks, and the subjects had a mean baseline body mass index of 28.22 $\pm$ 0.91. The objective of the trial was to assess the efficacy and safety of green coffee. The primary outcomes assessed were changes weight, body mass index, and percent body fat. Secondary outcomes were blood pressure and heart rate.

Few baseline characteristics were reported; mean weight and body mass index were 77 kg and 28 kg/m^2, respectively.[14] Following 22 weeks of treatment, the authors found a statistically significant difference in primary endpoints, favoring a beneficial effect of GCA in weight (−8.04g $\pm$ 2.31 kg), body mass index (−2.92 $\pm$ 0.85 kg/m^2), and percent body fat (−4.44 $\pm$ 2%) compared to baseline (mean 76.69 kg $\pm$ 9.91, 28.22 $\pm$0.91 kg/m^2, and 28.13% $\pm$ 4.95%). The authors concluded that GCA provides more weight loss than the US Food and Drug Administration–approved drugs on the market.

The primary limitation of this study was use of a crossover design. This study design is likely not optimal for measuring time-sensitive endpoints such as weight and body mass index. It is difficult to attribute weight loss to a specific dose or treatment, especially when the duration of each treatment arm was so brief. Evidence of this is shown in figures suggesting decreases in weight and body mass index were most dramatic during the first 6 weeks of treatment, regardless of treatment assignment. Additionally, the results in the

treatment group were statistically significant compared to baseline measurements, not a direct comparator, increasing risk for type I error. The milligram dose of caffeine in GCA was not identified, although it was stated that caffeine was included. Studies have shown that caffeine consumption can also decrease weight in patients and may also reduce the risk of developing metabolic syndrome. This makes it imperative to state the caffeine content so that weight loss can be attributed to the correct ingredient in GCA.[15,16] The study also had unclear blinding and lifestyle modifications. Finally, a specific primary endpoint and associated sample size calculations were not defined.

In a second prospective clinical trial, 62 volunteers were randomized to receive 4 weeks of Coffee Shape, a product with 81 mg of chlorogenic acid per serving, or Nescafe Expresso, a brewed coffee control.[17] Each group consumed 1 serving of assigned coffee per day. The objective of the study was to evaluate the effect that Coffee Shape has on weight. Outcome measures assessed were weight, waist, bust, and hip size. A primary outcome was not identified, and a sample size calculation was not conducted. Patients were advised to maintain their original diet and physical exercise; however, baseline information was not provided regarding this.

At baseline, patients in the treatment group had a mean starting weight of approximately 77 kg in both groups. After 4 weeks, patients in the treatment group had a mean reduction in weight by 1.35 $\pm$ 0.81 kg versus 0.12 $\pm$ 0.27 kg in placebo ($P < .05$). The average waist measurement decreased by 1.9 versus 0.01 inches, hips decreased by 1.3 versus 0.2 inches, and bust decreased by 1.25 versus 0.15 inches. Inferential statistics were only calculated for weight loss.

A notable limitation of this article is inconsistency of results presented. The raw data of reduction in weight and measurements for patients taking Coffee Shape differed in tables reporting the same endpoints, with no information identifying which numbers were used in statistical calculations. Additionally, the reported changes in bust, hip, and waist measurement are suspect considering patients only lost approximately 1.35 kg. No descriptive information regarding the measurement process was provided including blinding and consistency of those measuring the subjects. Coffee Shape is currently marketed in the United States but not recommended in patients with hypertension or diabetes; there were no criteria excluding these patients from the study. Finally, the clinical significance of an approximate 1 kg reduction in weight, relative to placebo, is minimal.

In a prospective clinical trial, 50 volunteers age 19 to 75 years were randomized in a 3:2 ratio to receive 60 days of treatment with Svetol, a capsular green coffee extract preparation, 200 mg orally twice daily or matching placebo.[19] Patients included in the study had a body mass index greater than 25 kg/m^2 and amenability to a "bland low caloric diet." Patients were excluded for history of gastrointestinal diseases, including cancer and infection, alcohol use, and use of medications for weight loss. The objectives of this study were to investigate whether Svetol could limit development of overweight and obesity, as well as related metabolic conditions. A primary endpoint was not identified.

Baseline characteristics of patients were not described, except for that they were similar in terms of weight and muscle mass to fat mass ratio.[18] Following 60 days of treatment, investigators report a reduction of 4.97 $\pm$ 0.32 kg in the treatment group compared to 2.45 $\pm$ 0.37 kg in the placebo group ($P < .001$). Body mass index was reduced by 1.9 $\pm$ 0.1 kg/m^2 in the treatment group and by 0.9 $\pm$ 0.1 kg/m^2 in the placebo group. It should be noted that all variability was presented as standard error of the mean. The authors found no difference in self-rating of physical appearance.

The primary limitation of this study is that authors did not describe whether investigators or participants were blinded to treatment assignment.[18] Additionally, the authors did not name a primary endpoint or perform a power calculation to determine sample size. Similarly, despite identifying study of development of overweight, obesity, and metabolic conditions as objectives of this study, the authors did not discuss any endpoints or results relating to these issues. The primary results discussed were changes in body weight, body mass index, and muscle mass to fat mass ratio. These results may be misleading as variability was described using standard error of the mean rather than standard deviation. Standard error of the mean produces small values that may cloud the true variability of study results. Very little information regarding baseline characteristics, such as weight, body mass index, presence of metabolic conditions, and so on, was provided. It is unclear whether the study results would apply to an overweight, obese, or morbidly obese population. Additionally, the authors did not address safety (eg, adverse event reporting) in their methods or results. Finally, the product was only assessed for 60 days, providing no information regarding long-term safety and efficacy. On a related note, the authors did not assess whether patients regained lost weight after discontinuing the product. The authors concluded that this product has a role in the management of obesity; however, the results do not address the limitations discussed.

In a prospective clinical trial, 30 volunteers were randomized in a 1:1 ratio to receive treatment with Coffee Slender, a coffee product with 200 mg green coffee extract per cup, or placebo as Nescafe Gold Norwegian blend coffee.[19] Each group consumed 5 cups of the assigned coffee per day for a total of 12 weeks. Patients included in the study were nonsmoking coffee drinkers with body mass index of 27.5 to 32 kg/m^2. The objective of this study was to evaluate the effect of green coffee extract on the overweight; a primary endpoint was not identified.

At baseline, patients in the treatment group had a mean starting weight of 85.2 $\pm$ 4.5 kg and body mass index of 29.2 $\pm$ 2.5 kg/m^2 compared to 84.3 $\pm$ 4.3 kg and 29.9 $\pm$ 2.4 kg/m^2 in the placebo group.[19] After 12 weeks, patients in the treatment group had a mean reduction in weight of 5.4 $\pm$ 0.6 kg ($P < .05$) and body mass index of 3.6 $\pm$ 0.3 kg/m^2 ($P < .05$) relative to baseline. Patients in the placebo group had a mean reduction in weight of 1.7 $\pm$ 0.9 kg and body mass index of 0.7 $\pm$ 0.4 kg/

m^2; neither of these results were statistically significant relative to baseline. No treatment-related adverse effects were reported.

As seen in the previous study, the primary limitation of this study is that authors did not describe whether study authors or participants were blinded to treatment assignment.[19] Additionally, the authors did not name a primary endpoint or perform a power calculation to determine sample size. Rather than directly comparing mean weight and body mass index between groups following 12 weeks of treatment, the authors compared the resulting mean values with baseline data for each group individually, increasing the risk for Type I error. Additionally, the authors indicated use of a Student *t* test (for parametric data) or Mann–Whitney test (for nonparametric data); tests designed to compare paired data would have been more appropriate. It should also be noted that the study only assessed overweight patients. These results would not apply to the obese or morbidly obese populations. Similar to the previous study, the authors only assessed use of green coffee for a 12-week period, leaving long-term safety and efficacy, as well as ability to maintain weight loss following discontinuation, as unanswered questions.

A meta-analysis evaluated 3 trials previously reviewed in this article (Coffee Shape, Svetol, and Coffee Slender).[10] The objective of this meta-analysis was to assess the efficacy of green coffee with regard to weight loss. There were significant differences between the 3 trials with regard to heterogeneity, with an I^2 statistic of 97%. Variable endpoints were conducted in individual trials, and therefore, the only data reported in this meta-analysis was weight loss. The analysis found a statistically significant difference with regard to body weight with a mean difference of −2.47 kg between green coffee and placebo (95% confidence interval = −4.23 to −0.72). The authors concluded that the clinical relevance is unknown and a more rigorous trial assessing the true efficacy of green coffee with regard to weight loss should be conducted.

A primary limitation of the meta-analysis is the variability of the included trials. Duration ranged from 4 to 12 weeks, and the daily dose of chlorogenic acid varied from 81 mg to 400 mg.[10] The variations in duration can significantly skew the data of this meta-analysis as weight may be considered time sensitive, with more cumulative weight loss over a greater amount of time. Thus, comparing the mean weight loss over differing durations yields a result that cannot be accurately interpreted. The meta-analysis included only trials that were double-blind and placebo controlled. However, 2 of the articles (Coffee Shape and Coffee Slender) used a potentially active comparator rather than a placebo, considering the possibility that caffeine can aid in weight loss. Additionally, the clinical trials stated that they were double-blinded, but on review, there was no description on whether investigators or participants were truly blinded. As stated in the GCA and Coffee Shape trials, data were inconsistent. Therefore, it should be noted that the accuracy of the meta-analysis data is uncertain as well.

Finally, the most publicized study of green coffee was conducted by *The Dr. Oz Show* where 100 women, aged 35 to 49 with body mass index of 25 to 45 kg/m^2 were either given 400 mg capsules of green coffee bean extract or placebo 3 times a day.[8] Participants were told to keep a journal of their food consumption and to not change their diet while on the study. Exclusion criteria included pregnancy, history of heart attack or stroke, and diabetes. The reported results were a mean loss of 2 pounds in the green coffee group, with an average loss of 1 pound in placebo over a 2-week time period. No other information regarding the trial is available. Beneficial information that was not provided includes whether or not there was randomization, blinding, or similar baseline characteristics, especially with regard to mean baseline weight of each group. It should also be noted that the dose used was higher than previous trials. The show concluded that green coffee could be beneficial for those 18 years or older, who are also healthy and wanting to lose weight. However, given the inclusion and exclusion criteria stated above, the recommendations from *The Dr. Oz Show* do not reflect the true external validity of the study.

Conclusion

Current literature regarding green coffee for the use of weight loss is limited to 4 small clinical trials. All studies found statistically significant reductions in weight compared to baseline or a direct comparator. However, in most studies, the clinical significance of this reduction was minimal. All these trials have significant limitations. Key limitations, overall, included lack of blinding, direct comparisons, and safety assessment. Additionally, the studies did not assess comprehensive endpoints, had very low sample size, and did not include lifestyle modifications. Finally, none of the studies assessed whether weight was regained on discontinuation. As seen in Table 2, when compared to the standards that the US Food and Drug Administration has set for trials looking at weight loss medications in order to properly assess safety and efficacy, the studies reviewed are below the benchmark of a properly designed trial. While adherence to US Food and Drug Administration guidelines is only one measure of study design appropriateness and other tools are available, it is a good baseline standard for weight loss studies. The clear deficiencies in the available literature make this a particularly relevant benchmark.

Well-designed trials demonstrating the efficacy and safety of green coffee for the use of weight loss are needed before it can be recommended for routine use. These trials should be powered to evaluate the efficacy of green coffee for weight loss in comparison to placebo or US Food and Drug Administration–approved medications, depending on the population studied, and should be double-blinded. Additionally, confounding factors such as diet and exercise should be described and equally conducted in treatment arms. Following published guidelines, lifestyle modifications should be initiated first in a patient interested in weight loss followed by pharmacotherapy that is US Food and Drug Administration approved. Green coffee extract is not recommended as a safe or effective treatment for weight loss.

Table 2. Comparison of US Food and Drug Administration Recommendations for Weight Loss Medications Versus Available Studies.

	Study Design	Duration	Primary Endpoint	Secondary Endpoints
FDA Recommendations[6]	Randomized, double-blind, placebo-controlled; >3000 receive active medication, >1500 receive placebo	1 year	Amount of weight loss; proportion of patients losing 5% of baseline weight versus placebo	Metabolic parameters
Vinson et al[14]	Randomized, double-blind, placebo-controlled, crossover; 16 patients	22 weeks	Weight, body mass index, percent body fat	Changes in blood pressure and heart rate
Ayton Global Research[17]	Randomized, double-blind; 62 volunteers	4 weeks	Weight	Waist, bust, and hip size
Dellalibera et al[18]	Randomized, placebo-controlled; 50 volunteers	60 days	Not identified	Not identified
Thom et al[19]	Randomized; 30 volunteers	12 weeks	Not identified	Not identified
The Dr. Oz Show[8]	100 female volunteers	Not identified	Weight	Not identified

Author Contributions

RDB generated the idea for this review. RDB and RB jointly designed and conducted the literature search, evaluated the studies, and analyzed the results.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study is exempt from oversight by human subjects research protection as there were no human subjects involved.

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EXHIBIT 5

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Review Article

The Use of Green Coffee Extract as a Weight Loss Supplement: A Systematic Review and Meta-Analysis of Randomised Clinical Trials

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The purpose of this paper is to assess the efficacy of green coffee extract (GCE) as a weight loss supplement, using data from human clinical trials. Electronic and nonelectronic searches were conducted to identify relevant articles, with no restrictions in time or language. Two independent reviewers extracted the data and assessed the methodological quality of included studies. Five eligible trials were identified, and three of these were included. All studies were associated with a high risk of bias. The meta-analytic result reveals a significant difference in body weight in GCE compared with placebo (mean difference: −2.47 kg; 95%CI: −4.23, −0.72). The magnitude of the effect is moderate, and there is significant heterogeneity amongst the studies. It is concluded that the results from these trials are promising, but the studies are all of poor methodological quality. More rigorous trials are needed to assess the usefulness of GCE as a weight loss tool.

1. Introduction

Overweight and obesity have become a serious health concern [1]. Different weight management strategies are presently utilised, and a variety of weight loss supplements sold as "slimming aids" are readily available. However, the efficacy of some of these food supplements remains uncertain. One such supplement is the green coffee extract (GCE).

GCE is present in green or raw coffee [2]. It is also present in roasted coffee, but much of the GCE is destroyed during the roasting process. Some GCE constituents, such as chlorogenic acid (CGA) can also be found in a variety of fruits and vegetables [3]. The daily intake of CGA in persons drinking coffee varies from 0.5 to 1 g [4]. The traditional method of extraction of GCE from green coffee bean, *Coffea canephora robusta*, involves the use of alcohol as a solvent [5]. Extracted GCE is marketed as a weight loss supplement under a variety of brand names as a weight loss supplement such as "Coffee Slender", and "Svetol".

Evidence is accumulating from animal studies regarding the use of GCE as a weight loss supplement [6, 7]. In human subjects, coffee intake has been reported to be inversely associated with weight gain [8]. Consumption of coffee has also been shown to produce changes in several glycaemic markers in older adults [9]. Similarly, other research has indicated that the consumption of caffeinated coffee can lead to some reductions in long-term weight gain, an effect which is likely to be due to the known thermogenic effects of caffeine intake as well as effects of GCE and other pharmacologically active substances present in coffee [10]. GCE has also been postulated to modify hormone secretion and glucose tolerance in humans [11]. This effect is accomplished by facilitating the absorption of glucose from the distal, rather than the proximal part of the gastrointestinal tract.

The objective of this paper is to analyse the results of human clinical trials assessing the efficacy of GCE as a weight-reducing agent.

2. Methods

Electronic searches of the literature were conducted for the following databases: MEDLINE, EMBASE, CINAHL, AMED, and *The Cochrane Library*. Each database was searched from inception up until April, 2010. Search terms used included coffee, green coffee, green coffee extract, roasted coffee, decaffeinated coffee, chlorogenic acid, caffeoylquinic acid, antiobesity agent, appetite suppressant, abdominal fat, BMI, body mass index, body fat, body weight, overweight, over weight, corpulen*, obes*, weight loss, weight decrease, weight watch, weight cycle, weight control, weight gain, weight maintenance, weight reduction, weight change, dietary supplement, food supplement, nutraceutical, nutri*supplement, over-the-counter OR OTC, nonprescription drugs, randomised controlled trial, clinical trial, and placebo. We also searched other internet databases for relevant conference proceedings, as well as our own files. Hand searches of the bibliography of retrieved full texts were also conducted.

Only randomised, double-blind, and placebo-controlled studies were included in this paper. To be considered for inclusion, studies had to test the efficacy of GCE for weight reduction in obese or overweight humans. Included studies also had to report body weight and/or body mass index (BMI) as an outcome. No age, time, or language restrictions were imposed for inclusion of studies. Studies which involved the use of GCE as part of a combination treatment or not involving obese or overweight subjects were excluded from this paper.

Two independent reviewers assessed the eligibility of studies to be included in the paper. Data were extracted systematically by two independent reviewers according to the patient characteristics, interventions, and results. The methodological quality of all included studies was assessed by the use of a quality assessment checklist adapted from the consolidated standard of reporting trials (CONSORT) guidelines [12, 13]. Disagreements were resolved through discussion with the third author.

Data are presented as means with standard deviations. Mean changes in body weight were used as common endpoints to assess the differences between GCE and placebo groups. Using the standard meta-analysis software [14], we calculated mean differences (MD) and 95% confidence intervals (CI). The I^2 statistic was used to assess for statistical heterogeneity amongst studies.

3. Results

Our searches produced 2160 "hits". 328 articles were excluded because they were duplicate citations, while 767 articles were excluded because of wrong titles and abstracts. Another 598 articles were excluded because they did not investigate a food supplements, and 454 articles excluded due to no report on clinical outcome. A further 13 articles were excluded due to unsuitable study design. Thus, 5 potentially relevant articles were identified (Figure 1). One trial was excluded because it involved only normal weight individuals, and did not measure weight as an outcome [15]. Another trial was excluded because it was not randomised [16]. In effect, 3 randomised clinical trials (RCTs) including a total of 142 participants met our inclusion criteria, and were included in this systematic paper [5, 17, 18]. Their key details are summarized in Tables 1 and 2.

A forest plot (random-effect model) for the three trials is shown in figure 2. The meta-analysis reveals a statistically significant difference in body weight between GCE and placebo (MD: −2.47 kg; 95% CI: −4.23, −0.72). The I^2 statistic of 97% suggests that there is considerable heterogeneity amongst the studies. A further plot of two trials which involved CGA-enriched GCE revealed a statistically nonsignificant difference in body weight between GCE and placebo (MD: −1.92 kg; 95% CI: −5.40, 1.56). Heterogeneity was also considerable in this analysis (I^2 statistic of 99%). One of the studies reported a statistically significant decrease in the percentage of body fat in the GCE group compared with baseline, but no significant difference in the placebo group [5]. There was no mention of intergroup differences regarding the percentage of body fat. None of the trials reported any adverse events associated with the use of GCE.

4. Discussion

The main purpose of this systematic paper was to assess the efficacy of GCE as a weight loss supplement. The overall meta-analysis revealed a significant difference in change in body weight between GCE and placebo. The magnitude of this significance is moderate, and the clinical relevance is therefore not certain. There is also considerable heterogeneity amongst the three trials.

In animals, GCE has been reported to influence postprandrial glucose concentration and blood lipid concentration [5]. This is thought to be via reduction in the absorption of glucose in the intestine; a mechanism achieved by promoting dispersal of the Na^+ electrochemical gradient. This dispersal leads to an influx of glucose into the enterocytes [19]. GCE is also thought to inhibit the enzymatic activity of hepatic glucose-6-phosphatase, which is involved in the homeostasis of glucose [20]. Reports from animal studies have suggested that GCE mediates its antiobesity effect possibly by suppressing the accumulation of hepatic triglycerides [6]. Some authors have also posited that the antiobesity effect of GCE may be mediated via alteration of plasma adipokine level and body fat distribution and downregulating fatty acid and cholesterol biosynthesis, whereas upregulating fatty acid oxidation and peroxisome proliferator-activated receptor alpha (PPARα) expression in the liver [7].

Diets rich in polyphenols may help to prevent various kinds of diseases associated with oxidative stress, including coronary heart disease and some forms of cancer [21, 22]. GCE has been reported to have antioxidant activity, demonstrated by its ability to scavenge free radicals *in vitro*, and to increase the antioxidant capacity of plasma *in vivo* [16, 23]. There is also evidence that certain dietary phenols, including GCE, may modify intestinal glucose uptake in a

Table 1: Methodological characteristics of included studies.

Author Year Country	Main outcome (s)	Main diagnoses of study participants	Study design	Gender M/F	Randomisation appropriate?	Allocation concealed?	Groups similar at baseline?	Similar follow-up of groups?	Outcome assessor blinded?	Care provider blinded?	Patients blinded?	Attrition bias?	ITT analysis?
*Ayton Research 2009 United Kingdom	Body weight, waist, bust and hip circumference	Healthy overweight subjects	Parallel	Unclear	?	?	+	+	?	?	?	?	?
Thom 2007 Norway	Body weight, body mass index	Slight to moderately overweight subjects	Parallel	12/18	?	?	+	+	?	?	?	–	–
Dellalibera 1998 France	Body weight, body mass index	Overweight volunteers	Parallel	Unclear	?	?	+	+	?	?	?	–	–

Abbreviation: ITT (intention-to-treat); M/F: Males/Females.
Symbols: *: Unpublished study, +: Yes, –: No, ?: Unclear.

Table 2: Main results of included RCTs[1].

Author Year	GCE specification	No. of participants randomised	Age in yrs; Sex: M/F	Body weight at baseline	Dosage of GCE	Treatment duration	Main results; reported as means with standard deviations	Adverse events	Control for lifestyle factors
Ayton Res. 2009 (unpublished)	CGA enriched green coffee	62	Not reported	76.65 ± 7.25 kg (GCE) 77.44 ± 12.93 kg (PLA)	180 mg daily	4 weeks	Weight loss was 1.35 ± 0.81 kg and 0.12 ± 0.27 kg for GCE and PLA respectively	Not reported	Normal lifestyle
Thom 2007	CGA enriched green coffee	30	Not reported 12/18	85.2 ± 4.5 kg (GCE) 84.3 ± 4.3 kg (PLA)	200 mg daily	12 weeks	Mean weight loss was 5.4 ± 0.6 kg (GCE) and 1.7 ± 0.9 kg (PLA). Mean fat loss was 3.6 ± 0.3% (GCE) and 0.7 ± 0.4% (PLA)	No adverse events	Regular diet, normal level of exercise
Dellalibera 2007	Green coffee extract	50	Range: 19–75	Not reported	200 mg daily	12 weeks	[2] Mean weight loss was 4.97 ± 0.32 kg and 2.45 ± 0.37 kg for GCE and PLA, respectively	Not reported	Not reported

Abbreviation: PLA: placebo

[1] Unless otherwise specified, values are reported as means with standard deviations.

[2] Values reported as means with standard errors.

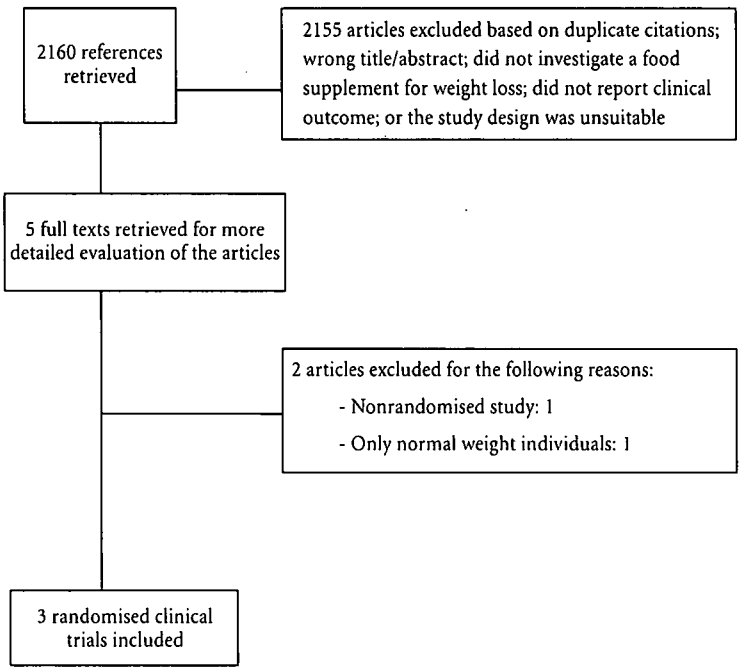

FIGURE 1: Flow chart for inclusion of randomised clinical trials.

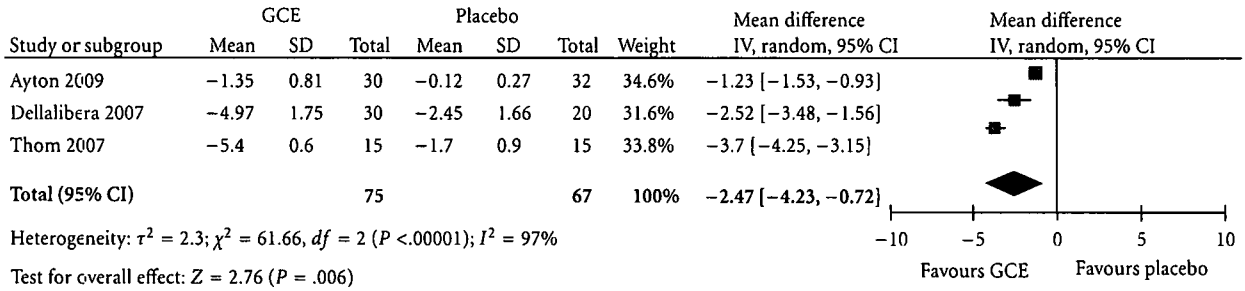

FIGURE 2: Forest plot showing the effect of GCE on body weight.

number of ways [8, 24]. This activity might provide a basis for explaining its effects on body weight. The purported slimming effect of GCE would have a protective effect against diabetes mellitus, via changes in gastrointestinal hormone secretion [10]. A few questions, however, arise from the RCTs which involve the use of GCE as a weight loss aid.

All the RCTs involving the use of GCE which have been conducted so far have very small sample sizes, with the largest number of participants being 62 in one trial [17]. These small sample sizes increase the possibility of spurious or false positive results. Two of the RCTs were unclear about drop-outs of participants from the trial; neither did they report on intention-to-treat analysis [17, 18]. All of the trials so far identified have been of very short duration. This makes it difficult to assess the efficacy and safety of GCE as a weight reduction agent on the medium to long-term. Although none of the RCTs identified reported any adverse events, this does not indicate that GCE intake is "risk-free". Two participants in a study report dropped out due to adverse events associated with the intake of GCE [16]. These included headache and urinary tract infection. Thus, the safety of this weight loss aid is not established.

The effective dosage of GCE for use as a weight loss supplement is also not established. The dosages of GCE reported in most of the human trials identified were estimated, as the GCE was a component of coffee. While 2 of the RCTs identified enriched their GCE with CGA [5, 17], the third trial did not report that the GCE used was fortified with CGA [18]. This warrants further investigation.

The RCTs identified from our searches were not also clear on blinding issues. None of the RCTs reported on how randomisation was carried out, and none provided information regarding blinding of outcome assessors. This casts doubt on the internal validity of these trials. Future trials involving the use of GCE as a weight loss supplement should be conducted in line with the CONSORT guidelines. This will ensure the validity and applicability of study results. Two authors in one study were affiliated to a company which markets Svetol [18] but did not specify whether or not they had any conflicts of interest.

This systematic review has several limitations. Though our search strategy involved both electronic and nonelectronic studies, we may not have identified all the available trials involving the use of GCE as a weight loss supplement. Furthermore, the methodological quality of the studies identified from our searches is poor, and all are of short duration. These factors prevent us from drawing firm conclusions about the effects of GCE on body weight.

5. Conclusion

The evidence from RCTs seems to indicate that the intake of GCE can promote weight loss. However, several caveats exist. The size of the effect is small, and the clinical relevance of this effect is uncertain. More rigorous trials with longer duration are needed to assess the efficacy and safety of GCE as a weight loss supplement.

Conflict of Interests

I. Onakpoya is funded by a grant from GlaxoSmithKline. The funder had no role in the preparation of the paper. R. Terry and E. Ernst declare no potential conflict of interests.

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EXHIBIT 0

EXHIBIT 6

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Supplements for Weight Loss: Hype or Help for Obesity? Part II. The Inside Scoop on Green Coffee Bean Extract

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Gerard E. Mullin, MD[1]

In this CAM Corner, we continue our discussion of a controversial subject—is there evidence to support the use of nutraceutical supplements in treating obesity? In the December 2014 CAM corner,[1] we discussed calcium, capsaicin, chitosan, chromium, *Citrus aurantium, Coleus forskohlii*, and conjugated linolenic acid. This CAM corner focuses on the most controversial supplement to date—green coffee bean extract.

Chlorogenic Acid (Green Coffee Bean Extract)

There is abundant literature to support the benefit of coffee, which seems to facilitate weight loss and prevent and/or improve a wide variety of chronic illnesses.[2–5] Evidence is accumulating from animal studies regarding the use of green coffee bean extract (GCBE) as a weight loss supplement. In human subjects, coffee intake has been reported to be inversely associated with weight gain, but a number of potential compounds in coffee can be attributed to its benefit.[6] Caffeine, phenolic compounds, or the combination of all can be contributing. However, it has been fairly well demonstrated that the synergistic interactions between several molecules give this coffee its health-promoting, weight loss power, with chlorogenic acid (CGA, aka GCBE) being the lead natural product. But is it the green coffee bean's chemical properties or the caffeine itself that is causing these effects? One research team addressed this question in a mouse model of obesity and insulin resistance,[7] demonstrating that decaffeinated green coffee bean extract prevented obesity and improved insulin resistance in these mice. Furthermore, they showed that the mechanism of action involved downregulation of genes that turn on fat cell formation and inflammation. And in a corroborating study, scientists demonstrated that decaffeinated GCBE liberates free fatty acids from fat cells, while yet another study showed that it decreases pancreatic fat-digesting enzyme activity, leaving intestinal fat potentially less digestible.[8]

A randomized placebo-controlled trial using 200 mg of CGA-enriched green coffee for 12 weeks was associated with a mean weight loss of 5.4 kg in the CGA group vs 0.6 kg in the placebo group.[9] In another study using a similar design, scientists observed that those who consumed 200 mg of GCBE daily for 12 weeks lost a mean of 5 kg vs 2.45 kg with placebo.[10] A meta-analysis published in the journal *Gastroenterology Research and Practice*[11] reviewed 2160 articles that were derived from using the search terms *green coffee bean extract* and *weight loss*. However, careful mining of these articles produced only 3 gold-standard studies that fit their inclusion criteria. The meta-analysis of 6 studies reveals a statistically significant difference in body weight between GCE and placebo (mean weight loss of 2.47kg).[12] However, the authors concluded, GCBE supplementation may be effective in promoting weight loss in overweight/obese subjects, but no effects were observed in normal weight subjects with mild hypertension. The paucity of data, inconsistent methodology, and low quality of currently available studies limited the conclusiveness of this analysis. Studies are needed to determine a mechanism of action for GCBE, and larger multisite clinical trials of high quality and consistent design are needed to elucidate the long-term effects and safety of GCBE supplementation on weight loss in normal weight, overweight, and obese subjects. These studies included a total of 142 participants, and the results were admittedly *promising*. Most important was their comment that "all studies were associated with a high risk of bias."[12]

Naturally, supplement manufacturers, marketers, TV doctors, and even Starbucks have featured the green coffee bean extract, advertising it as energizing weight loss magic bullets. However, the data to support this multimillion dollar market are not as "powerful" as they say.

A randomized, placebo-controlled trial of GCBE was published in the journal *Diabetes, Metabolic Syndrome, and Obesity* the year after the meta-analysis above came out, and it reported that GCBE may, indeed, help people lose weight.[13] This study was touted *heavily* by GCBE marketers to convince the public of its efficacy since these researchers claimed that those who used the supplement lost 16% of their body weight. But there were many problems with this study. Only 16 people participated in the study, which was conducted in India, written by researchers from the University of Scranton, and published in an open-access journal. Then on October, 22, 2014, the

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article was retracted by the U.S.-based research team, who "could not ensure the validity of the data."[14] A domino effect included a senate subcommittee hearing on Consumer Protection, Product Safety and Insurance on June 17, 2014, about the promotion of supplements for weight loss by Dr Oz and the sponsors of the study. Texas-based Applied Food Sciences settled with the Federal Trade Commission for only a $3.5 million fine for making false claims of a deeply flawed study that included their falsification of the data (ie, study duration, amount of weight loss by study subjects).[15,16] Many were duped by this study, as was Dr Oz, who was looking for a home run for his frustrated viewers who could not lose the weight.

Bottom line: Some evidence of the usefulness from longer-term studies with larger populations may corroborate the results above. For now, I cannot recommend this product. If you like coffee and want more chlorogenic acid, go with a lighter roast. Although darker roasts have less chlorogenic acid because roasting destroys this fat-burning natural product, they have lower levels of acrylamides (cancer-causing chemicals formed during the roasting process) than medium roasts.[17] That's why I personally choose the dark roasts to drink.

The next CAM corner will conclude our series on weight loss supplements and discuss how potential manipulation of the gut microbiome may hold the key to facilitating improvement of metabolism and weight regulation.

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EXHIBIT 7

EXHIBIT 7

European Food Safety Authority EFSA Journal 2011;9(4):2057

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to coffee, including chlorogenic acids from coffee, and protection of DNA, proteins and lipids from oxidative damage (ID 1099, 3152, 4301), maintenance of normal blood glucose concentrations (ID 1100, 1962), and contribution to the maintenance or achievement of a normal body weight (ID 2031, 4326) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006. This opinion addresses the scientific substantiation of health claims in relation to coffee and protection of DNA, proteins and lipids from oxidative damage, maintenance of normal blood glucose concentrations, and contribution to the maintenance or achievement of a normal body weight. The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The foods/food constituents that are the subject of the health claims are coffee, *Coffea Arabica* L., chlorogenic acids from coffee, and antioxidants in coffee. The Panel considers that whereas coffee and antioxidants in coffee are not sufficiently characterised in relation to the claimed effects, chlorogenic acids from coffee are sufficiently characterised.

[1] On request from the European Commission, Question No EFSA-Q-2008-1838, EFSA-Q-2008-1839, EFSA-Q-2008-2695, EFSA-Q-2008-2764, EFSA-Q-2008-3884, EFSA-Q-2010-00254, EFSA-Q-2010-00279, adopted on 28 January 2011.

[2] Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank for the preparatory work on this scientific opinion: The members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen. The members of the Claims Sub-Working Group on Cardiovascular Health/Oxidative Stress: Antti Aro, Marianne Geleijnse, Marina Heinonen, Ambroise Martin, Wilhelm Stahl and Henk van den Berg. The members of the Claims Sub-Working Group on Weight Management/Satiety/ Glucose and Insulin Control/Physical Performance: Kees de Graaf, Joanne Harrold, Mette Hansen, Mette Kristensen, Anders Sjödin and Inge Tetens.

Suggested citation: EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to coffee, including chlorogenic acids from coffee, and protection of DNA, proteins and lipids from oxidative damage (ID 1099, 3152, 4301), maintenance of normal blood glucose concentrations (ID 1100, 1962), and contribution to the maintenance or achievement of a normal body weight (ID 2031, 4326) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(4):2057. [23 pp.]. doi:10.2903/j.efsa.2011.2057. Available online: www.efsa.europa.eu/efsajournal

Protection of DNA, proteins and lipids from oxidative damage

The claimed effects are "protection of body tissues, lipids, cells and DNA from oxidative damage", "oxidative stress reduction" and "coffee naturally contains antioxidants that may support the body's natural cell defences". The target population is assumed to be the general population. The Panel considers that protection of DNA, proteins and lipids from oxidative damage may be a beneficial physiological effect.

The Panel considers that the human studies provided did not use suitable markers to assess oxidative damage *in vivo*. The Panel also notes that in most of the studies provided coffee was not sufficiently characterised in relation to the claimed effect, and that its content of chlorogenic acids was not reported. The Panel considers that evidence provided in *in vitro* studies is not sufficient to predict the occurrence of an effect of coffee consumption on protection of DNA, lipids or proteins from oxidative damage *in vivo* in humans.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of chlorogenic acids from coffee and protection of DNA, lipids or proteins from oxidative damage.

Maintenance of normal blood glucose concentrations

The claimed effect is "glucose homeostasis". The target population is assumed to be the general population. In the context of the proposed wordings, the Panel assumes that the claimed effect refers to the long-term maintenance of normal blood glucose concentrations. The Panel considers that long-term maintenance of normal blood glucose concentrations is a beneficial physiological effect.

The Panel considers that in the studies provided coffee was not sufficiently characterised in relation to the claimed effect, and/or that outcome measures were not appropriate to assess the long-term maintenance of normal blood glucose concentrations.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of chlorogenic acids in coffee and maintenance of normal blood glucose concentrations.

Contribution to the maintenance or achievement of a normal body weight

The claimed effects are "weight loss and weight control in overweight adults/reduces glucose absorption from gut" and "promotes weight-loss and weight-control in overweight healthy adults by reducing glucose uptake in the gastrointestinal system/absorbance from the gut (by regulating glucose homeostasis in the liver, thus promoting the use as fat as a source of energy in the body)". The target population is assumed to be the general population. In the context of the proposed wordings, the Panel assumes that the claimed effects refer to body weight control. The Panel considers that contribution to the maintenance or achievement of a normal body weight is a beneficial physiological effect.

No references were provided from which conclusions could be drawn for the scientific substantiation of the claimed effect.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of chlorogenic acids from coffee and contribution to the maintenance or achievement of a normal body weight.

KEY WORDS

Coffee, oxidative damage, blood glucose, weight management, health claims.

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INFORMATION AS PROVIDED IN THE CONSOLIDATED LIST

The consolidated list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006[4] submitted by Member States contains main entry claims with corresponding conditions of use and literature for similar health claims. EFSA has screened all health claims contained in the original consolidated list of Article 13 health claims which was received by EFSA in 2008 using six criteria established by the NDA Panel to identify claims for which EFSA considered sufficient information had been provided for evaluation and those for which more information or clarification was needed before evaluation could be carried out[5]. The clarifications which were received by EFSA through the screening process have been included in the consolidated list. This additional information will serve as clarification to the originally provided information. The information provided in the consolidated list for the health claims which are the subject of this opinion is tabulated in Appendix C.

ASSESSMENT

1. Characterisation of the food/constituent

The foods/food constituents that are the subjects of the health claims are coffee, *Coffea Arabica* L., chlorogenic acids from coffee, and antioxidants in coffee.

Coffee contains a wide range of "bioactive" compounds including caffeine and other purine derivatives, polyphenolic compounds such as chlorogenic acid derivatives and its degradation product caffeic acid, and specific diterpenes such as kahweol and cafestol. No information is provided on the concentration of such compounds in coffee, but this will likely depend on the coffee variety, on the roasting of the beans and on the brewing process, such as the use of coffee filters. Also, no specifications were provided on the compounds or molecules generically referred to as "antioxidants in coffee".

The Panel notes that chlorogenic acid from coffee has been specified as the "active" food constituent responsible for the claimed effects considered in this opinion. Chlorogenic acids from coffee are well defined compounds which can be measured in foods by established methods.

The Panel considers that whereas the food/food constituents, coffee and antioxidants in coffee, are not sufficiently characterised in relation to the claimed effects evaluated in this opinion, the food constituent, chlorogenic acids from coffee, is sufficiently characterised.

2. Relevance of the claimed effect to human health

2.1. Protection of DNA, proteins and lipids from oxidative damage (ID 1099, 3152, 4301)

The claimed effects are "protection of body tissues, lipids, cells and DNA from oxidative damage", "oxidative stress reduction" and "coffee naturally contains antioxidants that may support the body's natural cell defences". The Panel assumes that the target population is the general population.

Reactive oxygen species (ROS) including several kinds of radicals are generated in biochemical processes (e.g. respiratory chain) and as a consequence of exposure to exogenous factors (e.g. radiation and pollutants). These reactive intermediates damage molecules such as DNA, proteins

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

[5] Briefing document for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims: http://www.efsa.europa.eu/en/ndameetings/docs/nda100601-ax01.pdf

and lipids if they are not intercepted by the antioxidant network which includes radical scavengers like antioxidant nutrients.

The Panel considers that protection of DNA, proteins and lipids from oxidative damage may be a beneficial physiological effect.

2.2. Maintenance of normal blood glucose concentrations (ID 1100, 1962)

The claimed effect is "glucose homeostasis". The Panel assumes that the target population is the general population.

In the context of the proposed wordings, the Panel assumes that the claimed effect refers to the long-term maintenance of normal blood glucose concentrations.

The Panel considers that long-term maintenance of normal blood glucose concentrations is a beneficial physiological effect.

2.3. Contribution to the maintenance or achievement of a normal body weight (ID 2031, 4326)

The claimed effects are "weight loss and weight control in overweight adults/reduces glucose absorption from gut" and "promotes weight-loss and weight-control in overweight healthy adults by reducing glucose uptake in the gastrointestinal system/absorbance from the gut (by regulating glucose homeostasis in the liver, thus promoting the use as fat as a source of energy in the body)". The Panel assumes that the target population is the general population.

In the context of the proposed wordings, the Panel assumes that the claimed effects refer to body weight control.

Weight management can be interpreted as the contribution to maintenance of a normal body weight. In this context, weight loss in overweight subjects without achieving a normal body weight is considered to be a beneficial physiological effect.

The Panel considers that contribution to the maintenance or achievement of a normal body weight is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

3.1. Protection of DNA, proteins and lipids from oxidative damage (ID 1099, 3152, 4301)

Some of the references provided in the consolidated list reported on the association between coffee drinking and disease risk (e.g. hepatocellular carcinoma, liver cirrhosis, breast cancer, colon cancer, and inflammatory and cardiovascular disease) in observational (cohort) studies. Other references were general reviews on claim substantiation, on biomarkers for chronic disease risk, on the chemistry and absorption of chlorogenic acids and other polyphenols from coffee, and on the effects of coffee drinking on liver enzyme activity (a marker of liver damage), and on endothelial and vascular function. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claimed effect.

Some experimental, and generally small-scale, human intervention studies on the effects of coffee consumption, or of individual compounds present in coffee, on markers of antioxidant status (e.g. antioxidant activity/capacity/potential of plasma (Natella et al., 2002)), on the induction of antioxidant enzymes such as super-oxide dismutase (SOD) or glutathione S-transferases (GSTA and

GSTP) and/or on plasma concentrations of glutathione (GSH) (Bichler et al., 2007; Esposito et al., 2003; Grubben et al., 2000; Mursu et al., 2005; Steinkellner et al., 2005), on the formation of malondialdehyde (MDA), on thiobarbituric acid reactive substances (TBARS), and/or on LDL oxidation lag time (Mursu et al., 2005; Yukawa et al., 2004) were provided. The Panel notes that measurements of the total antioxidant activity/potential of plasma are not considered as markers of oxidative damage, and that the formation of TBARS or of MDA assessed by colorimetric assays, as well as the resistance of LDL to oxidation, are not suitable markers to assess lipid peroxidation (Dalle-Donne et al., 2006; Dragsted, 2008; Griffiths et al., 2002; Knasmuller et al., 2008; Mayne, 2003). Also two small intervention studies on the effects of coffee consumption on DNA damage measured *ex vivo* in lymphocytes using single cell gel electrophoresis (Comet assay) after incubation with restriction enzymes and treatment with H_2O_2 or a heterocyclic compound (Bichler et al., 2007), and on benzo[a]pyrene diolepoxide (BPDE) induced DNA-migration using the Comet assay (Steinkellner et al., 2005), were presented. The Panel notes that these measurements do not provide information about oxidative damage to DNA *in vivo* (Dusinska and Collins, 2008). The Panel also notes that coffee has not been sufficiently characterised in these studies in relation to the claimed effect, and that its content of chlorogenic acids has not been reported. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claimed effect.

In a multiple-dose supplementation trial, 43 healthy non-smoking men consumed daily either no coffee, 3 cups (450 mL) or 6 cups (900 mL) of filtered coffee (7–8 g of grounds per 150 mL cup) for three weeks. *In vivo* LDL oxidation using conjugated dienes, plasma hydroxy fatty acids, activity of antioxidant enzymes, and plasma F2-isoprostanes were assessed (Mursu et al., 2005). The Panel notes that coffee has not been sufficiently characterised in this study in relation to the claimed effect, and that its content of chlorogenic acids has not been reported. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claimed effect.

Data from *in vitro* studies on the effect of caffeic acid on LDL resistance to oxidation (lag time), and on glutathione (GSH) depletion (Nardini et al., 1995; 1997; Richelle et al., 2001), and studies on the chemopreventive effects of chlorogenic acids in human cancer cell lines, on transcription factors and biomarkers of cell proliferation (Bandyopadhyay et al., 2004; Feng et al., 2005), and on the effects of kahweol and cafestol on induced DNA damage in cultured NIH3T3 cells (Lee and Jeong, 2007), were submitted. The Panel considers that evidence provided in *in vitro* studies is not sufficient to predict the occurrence of an effect of coffee on protection of DNA, lipids or proteins from oxidative damage *in vivo* in humans.

The Panel concludes that a cause and effect relationship has not been established between the consumption of chlorogenic acids from coffee and protection of DNA, lipids or proteins from oxidative damage.

3.2. Maintenance of normal blood glucose concentrations (ID 1100, 1962)

Some of the references provided for the substantiation of the claim reported on the association between coffee drinking and disease risk (e.g. type II diabetes, gestational diabetes, metabolic disease, cardiovascular disease) in observational (cohort) studies, and on the effects of chlorogenic acids on various aspects of glucose metabolism (enzymes and transporter proteins). Other references included reviews on the dietary sources of chlorogenic acids, and on magnesium supplementation in diabetes. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claimed effect.

Five references reported on human intervention studies which investigated the effects of coffee consumption on either post-prandial glycaemic and insulinaemic responses (Battram et al., 2006; Feinberg et al., 1968; Johnston et al., 2003; Keijzers et al., 2002), or on plasma C-peptide

concentrations (Wu et al., 2005). The Panel considers that no conclusions can be drawn from these outcome measures in relation to the long-term maintenance of normal blood glucose concentrations.

Two references reported on human intervention studies which addressed the effects of coffee consumption during two to four weeks on fasting glucose and insulin concentrations (Naismith et al., 1970; van Dam et al., 2004). Another reference reported on a cross-sectional study which investigated the association between coffee intake and glucose tolerance and insulin secretion during an oral glucose tolerance test (Bidel et al., 2006). In all of these studies, coffee was not sufficiently characterised in relation to the claimed effect, and outcome measures were not appropriate to assess the long-term maintenance of normal blood glucose concentrations. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claimed effect.

The Panel concludes that a cause and effect relationship has not been established between the consumption of chlorogenic acids from coffee and maintenance of normal blood glucose concentrations.

3.3. Contribution to the maintenance or achievement of a normal body weight (ID 2031, 4326)

A number of references on the bioavailability of chlorogenic acids, on the effects of coffee and chlorogenic acids on blood glucose control, and on the effects of chlorogenic acids in animal and *in vitro* models with respect to mutagenicity, antioxidant capacity and inhibition of hepatic glucose-6-phosphatase have been provided. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claimed effect.

A randomised, controlled trial investigated the effects of an instant coffee containing a green coffee extract (200 mg of extract per 2200 mg of coffee) with a high content of chlorogenic acids (i.e. 90-100 mg of chlorogenic acids per 200 mg of green coffee extract with equal amounts of the three isomers 5-, 4-, and 3-caffeoylquinic acid) and <2 % caffeine with no cafestol or kahweol *vs.* regular decaffeinated instant coffee containing 30-40 mg of chlorogenic acid per g of coffee on body weight in 30 overweight adults (Thom, 2007). Participants selected were overweight, non-smokers, and not taking medication on a regular basis for the treatment of chronic diseases, and were asked to maintain their usual diet and physical activity or exercise programmes. Subjects consumed 11 g of the test coffee per day (n=15) or 11 g of the control coffee per day (n=15), in both cases as black coffee, for 12 weeks, and were followed up for one and three months after the end of the study. The Panel notes the small sample size of the study, and that the background diet and physical activity at baseline, along with changes during the study, were not assessed and/or reported, for which reason it is unclear whether intervention and control groups were comparable for these variables. The Panel notes the important methodological limitations of the study and considers that no conclusions can be drawn from this study for the scientific substantiation of the claimed effect.

Another randomised, placebo-controlled human intervention study on the effects of a green coffee extract (200 mg of extract per capsule) containing chlorogenic acids (i.e. 90-100 mg per capsule with equal amounts of the three isomers 5-, 4-, and 3-caffeoylquinic acid) and <2 % caffeine with no cafestol and kahweol *vs.* placebo (maltodextrin) on body weight in overweight and obese subjects (males and females aged 19 to 75 years) was provided (Dellalibera et al., 2006). Participants were randomised to consume two capsules daily of the green coffee extract (n=30) or placebo (n=20) with the main meal for 60 days in the context of a "mildly hypocaloric diet". The Panel notes that, although the authors reported that the intervention and placebo groups were "homogeneous with respect to body weight and fat-free mass to fat mass ratio", the baseline characteristics of participants in both groups were not provided, and that whether these groups were comparable for other variables (e.g. age and sex distribution) was not reported. The Panel also notes that the background diet and physical activity at baseline and during the intervention were not reported, and that no details were given with

respect to the "mildly hypocaloric diet" prescribed during the study, nor on whether (and how) compliance with dietary advice was checked. The Panel notes the important methodological limitations of the study and considers that no conclusions can be drawn from this study for the scientific substantiation of the claimed effect.

The Panel concludes that a cause and effect relationship has not been established between the consumption of chlorogenic acids from coffee and contribution to the maintenance or achievement of a normal body weight.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food/food constituents, coffee and antioxidants in coffee, which are the subjects of the health claims, are not sufficiently characterised in relation to the claimed effects evaluated in this opinion, whereas chlorogenic acids from coffee are sufficiently characterised.

Protection of DNA, proteins and lipids from oxidative damage (ID 1099, 3152, 4301)

- The claimed effects are "protection of body tissues, lipids, cells and DNA from oxidative damage", "oxidative stress reduction" and "coffee naturally contains antioxidants that may support the body's natural cell defences". The target population is assumed to be the general population. Protection of DNA, proteins and lipids from oxidative damage may be a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of chlorogenic acids from coffee and protection of DNA, lipids or proteins from oxidative damage.

Maintenance of normal blood glucose concentrations (ID 1100, 1962)

- The claimed effect is "glucose homeostasis". The target population is assumed to be the general population. Long-term maintenance of normal blood glucose concentrations is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of chlorogenic acids from coffee and maintenance of normal blood glucose concentrations.

Contribution to the maintenance or achievement of a normal body weight (ID 2031, 4326)

- The claimed effects are "weight loss and weight control in overweight adults/reduces glucose absorption from gut" and "promotes weight-loss and weight-control in overweight healthy adults by reducing glucose uptake in the gastrointestinal system/absorbance from the gut (by regulating glucose homeostasis in the liver, thus promoting the use as fat as a source of energy in the body)". The target population is assumed to be the general population. Contribution to the maintenance or achievement of a normal body weight is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of chlorogenic acids from coffee and contribution to the maintenance or achievement of a normal body weight.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-1838, EFSA-Q-2008-1839, EFSA-Q-2008-2695, EFSA-Q-2008-2764, EFSA-Q-2008-3884, EFSA-Q-2010-00254, EFSA-Q-2010-00279). The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The full list of supporting references as provided to EFSA is available on: http://www.efsa.europa.eu/panels/nda/claims/article13.htm.

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APPENDICES

APPENDIX A

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Regulation (EC) No 1924/2006 on nutrition and health claims made on foods[6] (hereinafter "the Regulation") entered into force on 19th January 2007.

Article 13 of the Regulation foresees that the Commission shall adopt a Community list of permitted health claims other than those referring to the reduction of disease risk and to children's development and health. This Community list shall be adopted through the Regulatory Committee procedure and following consultation of the European Food Safety Authority (EFSA).

Health claims are defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

In accordance with Article 13 (1) health claims other than those referring to the reduction of disease risk and to children's development and health are health claims describing or referring to:

a) the role of a nutrient or other substance in growth, development and the functions of the body; or

b) psychological and behavioural functions; or

c) without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

To be included in the Community list of permitted health claims, the claims shall be:

(i) based on generally accepted scientific evidence; and

(ii) well understood by the average consumer.

Member States provided the Commission with lists of claims as referred to in Article 13 (1) by 31 January 2008 accompanied by the conditions applying to them and by references to the relevant scientific justification. These lists have been consolidated into the list which forms the basis for the EFSA consultation in accordance with Article 13 (3).

ISSUES THAT NEED TO BE CONSIDERED

IMPORTANCE AND PERTINENCE OF THE FOOD[7]

Foods are commonly involved in many different functions[8] of the body, and for one single food many health claims may therefore be scientifically true. Therefore, the relative importance of food e.g. nutrients in relation to other nutrients for the expressed beneficial effect should be considered: for functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

[6] OJ L12, 18/01/2007
[7] The term 'food' when used in this Terms of Reference refers to a food, the food or the food category.
[8] The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

It should also be considered if the information on the characteristics of the food contains aspects pertinent to the beneficial effect.

SUBSTANTIATION OF CLAIMS BY GENERALLY ACCEPTABLE SCIENTIFIC EVIDENCE

Scientific substantiation is the main aspect to be taken into account to authorise health claims. Claims should be scientifically substantiated by taking into account the totality of the available scientific data, and by weighing the evidence, and shall demonstrate the extent to which:

(a) the claimed effect of the food is beneficial for human health,

(b) a cause and effect relationship is established between consumption of the food and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet,

(d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

EFSA has mentioned in its scientific and technical guidance for the preparation and presentation of the application for authorisation of health claims consistent criteria for the potential sources of scientific data. Such sources may not be available for all health claims. Nevertheless it will be relevant and important that EFSA comments on the availability and quality of such data in order to allow the regulator to judge and make a risk management decision about the acceptability of health claims included in the submitted list.

The scientific evidence about the role of a food on a nutritional or physiological function is not enough to justify the claim. The beneficial effect of the dietary intake has also to be demonstrated. Moreover, the beneficial effect should be significant i.e. satisfactorily demonstrate to beneficially affect identified functions in the body in a way which is relevant to health. Although an appreciation of the beneficial effect in relation to the nutritional status of the European population may be of interest, the presence or absence of the actual need for a nutrient or other substance with nutritional or physiological effect for that population should not, however, condition such considerations.

Different types of effects can be claimed. Claims referring to the maintenance of a function may be distinct from claims referring to the improvement of a function. EFSA may wish to comment whether such different claims comply with the criteria laid down in the Regulation.

WORDING OF HEALTH CLAIMS

Scientific substantiation of health claims is the main aspect on which EFSA's opinion is requested. However, the wording of health claims should also be commented by EFSA in its opinion.

There is potentially a plethora of expressions that may be used to convey the relationship between the food and the function. This may be due to commercial practices, consumer perception and linguistic or cultural differences across the EU. Nevertheless, the wording used to make health claims should be truthful, clear, reliable and useful to the consumer in choosing a healthy diet.

In addition to fulfilling the general principles and conditions of the Regulation laid down in Article 3 and 5, Article 13(1)(a) stipulates that health claims shall describe or refer to "the role of a nutrient or other substance in growth, development and the functions of the body". Therefore, the requirement to

describe or refer to the 'role' of a nutrient or substance in growth, development and the functions of the body should be carefully considered.

The specificity of the wording is very important. Health claims such as "Substance X supports the function of the joints" may not sufficiently do so, whereas a claim such as "Substance X helps maintain the flexibility of the joints" would. In the first example of a claim it is unclear which of the various functions of the joints is described or referred to contrary to the latter example which specifies this by using the word "flexibility".

The clarity of the wording is very important. The guiding principle should be that the description or reference to the role of the nutrient or other substance shall be clear and unambiguous and therefore be specified to the extent possible i.e. descriptive words/ terms which can have multiple meanings should be avoided. To this end, wordings like "strengthens your natural defences" or "contain antioxidants" should be considered as well as "may" or "might" as opposed to words like "contributes", "aids" or "helps".

In addition, for functions affected by a large number of dietary factors it should be considered whether wordings such as "indispensable", "necessary", "essential" and "important" reflects the strength of the scientific evidence.

Similar alternative wordings as mentioned above are used for claims relating to different relationships between the various foods and health. It is not the intention of the regulator to adopt a detailed and rigid list of claims where all possible wordings for the different claims are approved. Therefore, it is not required that EFSA comments on each individual wording for each claim unless the wording is strictly pertinent to a specific claim. It would be appreciated though that EFSA may consider and comment generally on such elements relating to wording to ensure the compliance with the criteria laid down in the Regulation.

In doing so the explanation provided for in recital 16 of the Regulation on the notion of the average consumer should be recalled. In addition, such assessment should take into account the particular perspective and/or knowledge in the target group of the claim, if such is indicated or implied.

TERMS OF REFERENCE

HEALTH CLAIMS OTHER THAN THOSE REFERRING TO THE REDUCTION OF DISEASE RISK AND TO CHILDREN'S DEVELOPMENT AND HEALTH

EFSA should in particular consider, and provide advice on the following aspects:

- Whether adequate information is provided on the characteristics of the food pertinent to the beneficial effect.
- Whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence by taking into account the totality of the available scientific data, and by weighing the evidence. In this context EFSA is invited to comment on the nature and quality of the totality of the evidence provided according to consistent criteria.
- The specific importance of the food for the claimed effect. For functions affected by a large number of dietary factors whether a reference to a single food is scientifically pertinent.

In addition, EFSA should consider the claimed effect on the function, and provide advice on the extent to which:

- the claimed effect of the food in the identified function is beneficial.
- a cause and effect relationship has been established between consumption of the food and the claimed effect in humans and whether the magnitude of the effect is related to the quantity consumed.
- where appropriate, the effect on the function is significant in relation to the quantity of the food proposed to be consumed and if this quantity could reasonably be consumed as part of a balanced diet.
- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.
- the wordings used to express the claimed effect reflect the scientific evidence and complies with the criteria laid down in the Regulation.

When considering these elements EFSA should also provide advice, when appropriate:

- on the appropriate application of Article 10 (2) (c) and (d) in the Regulation, which provides for additional labelling requirements addressed to persons who should avoid using the food; and/or warnings for products that are likely to present a health risk if consumed to excess.

APPENDIX B

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the food, a positive assessment of its safety, nor a decision on whether the food is, or is not, classified as foodstuffs. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wordings of the claims and the conditions of use as proposed in the Consolidated List may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 13(3) of Regulation (EC) No 1924/2006.

APPENDIX C

Table 1. Main entry health claims related to coffee, including chlorogenic acids from coffee, including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food component	Health Relationship	Proposed wording
1099	Coffee	Protection of body tissues, lipids, cells and DNA from oxidative damage.	Coffee is a major dietary source of antioxidants. Antioxidants from dietary sources: protect you from free radicals; protect your cells and tissues from oxidation; antioxidants help strengthen our body's natural defences against oxidative stress.
	Conditions of use - 1 or 2 cups per day. - A coffee drink made by the filter method and diffusing 7g of ground coffee in 100 mL of water, 8.8 g/125 mL (dose), 35 g/500 mL (daily dose). - The coffee drink contains antioxidants, including 80-100 mg/100 mL of caffeine and approximately 116 mg/100 mL of chlorogenic acids. - 2 Tassen pro Tag.		
ID	**Food or Food component**	**Health Relationship**	**Proposed wording**
1100	Coffee	Glucose homeostasis.	coffee contributes to healthy lood glucose levels.
	Conditions of use - 4 tassen pro tag. - 3 cups per day. - A coffee drink made by filtering roasted coffee and diffusing 7 g of ground coffee in 100 mL of water, 8.8 g/125 mL (dose), 35 g/500 mL (daily dose).		
ID	**Food or Food component**	**Health Relationship**	**Proposed wording**
1962	Chlorogenic acids from Coffee	Glucose homeostasis	Chlorogenic acids from coffee extract contributes to keep normal blood glucose levels; Chlorogenic acids from coffee extract has a beneficial effect on glucose metabolism/ insulin metabolism.
	Conditions of use 400 mg/day coffee extract containing 45 % chlorogenic acids.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
2031	CoffeeSLENDER® Tablets made from an extract from	i). Weight loss and weight control in overweight	i). As an aid to weight loss and weight control as part of a calorie

	green coffee beans (Svetol®) the active principle of which is:-=5-caffeoylquinic acid or (Chlorogenic acid) =45%, Caffeine = 2%, 3-caffeoylquinic acid =10%	adults. ii). Reduces glucose absorption from gut.	controlled diet. ii). Acts by reducing absorption of sugar (glucose) from the digestive tract.
	Conditions of use - Three tablets to be taken daily.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
3152	Antioxidants in coffee	Oxidative stress reduction	Antioxidants in coffee helps protect our cells against free radicals.
	Conditions of use - 1 - 2 cups/ day		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
4301	Name of Food product: coffee Description of food in terms of food legislation categories: food not covered by specific food legislation Was food on Irish market before 1st July 2007: Yes	Health benefits of food: Coffee naturally contains antioxidants that may support the body's natural cell defences Do benefits relate to a disease risk factor: No Target group: All adults aged 18 years and over	Exact wording of claim as it appears on product: Coffee naturally contains antioxidants, that may support the body's natural cell defences. Examples of any alternative wording that may be used in relation to claim: Coffee is a major dietary source of antioxidants. Antioxidants from dietary sources: protect from free radicals which cause cell damage; protect body tissues, lipids, cells and DNA from oxidative damage; help strengthen the body's natural defences against oxidative stress. Is claim a picture: Yes Description of picture: A coffee bean
	Conditions of use - Number of nutrients/other substances that are essential to claimed effect: 1. Names of nutrient/other substances and Quantity in Average daily serving: 162mg chlorogenic acids (CGA). Weight of average daily food serving: 162 miligram(s). Daily amount to be consumed to produce claimed effect: 162 miligram(s). Number of food portions this equates to in everyday food portions: 3. Are there factors that could interfere with bioavailability: No. Length of time after consumption for claimed effect to become apparent: There are short-term and long-term effects. Is there a limit to the amount of food which should be consumed in order to avoid adverse health effects: Yes. State the maximum limit in mg/kg body weight/day: 300.00. Potential adverse health effects: It may produce various effects, depending on if a person has caffeine sensitivity. Describe subgroups this limit applies to: pregnant women and people sensitive to caffeine. Other conditions for use: Polyphenols are the most abundant antioxidants in our diets. Coffee beans contain a range of polypehenol		

	antioxidants with chlorogenic aces (CGA) being one of the richest dietary sources of CGA.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
4326	Decaffeinated green (unroasted) coffee bean extract produced from Coffea canephora robusta (plant:extract ratio between 6:1 to 8:1). The active ingredients contained in the green coffee extract are chlorogenic acids (>45% w/w). The chlorogenic acids mainly comprise the 3 isomers of caffeoylquinic acid, 3 caffeoylquinic acid, 4-caffeoylquinic acid, and 5-caffeoylquinic acid. The green coffee extract also contains dicaffeoylquinic acids (3,4-, 3,5-, and 4,5-dicaffeoylquinic acid) and feruloylquinic acids (3-, 4-, and 5-feruloylquinic acid) at levels of 9.6 and 13.2% of total chlorogenic acids, respectively. Example of Specifications for Decaffeinated Green Coffee Extract. Specification Parameter Specification. Appearance Fine powder Colour Yellow. Flavour Characteristic Identification (UV profile in methanol) Maximum at 325 ± 5 nm. Particle size 60 to 400 mesh. Total polyphenols 50 to 55%. Total chlorogenic acids 45 to 50%. 5-Caffeoylquinic acid 10 to 15% 5-Caffeoylquinic acid/total chlorogenic acid ratio 0.2 to 0.3. Caffeine Less than 2%.	Promotes weight-loss and weight-control in overweight healthy adults by reducing glucose uptake in the gastrointestinal system/absorbance from the gut (by regulating glucose homeostasis in the liver, thus promoting the use as fat as a source of energy in the body).	As an aid to weight loss and weight control as part of a calorie controlled diet. Acts by reducing absorption of sugar (glucose) from the digestive tract.

	More detailed compositional data is available upon request.		
	Conditions of use - 400 to 1000 mg per day. - The daily recommended dose can be reached in a single or multiple administrations. - The product can be taken alone (i.e. in capsules), or integrated to a food matrix (i.e. soluble coffee beverage).		

GLOSSARY AND ABBREVIATIONS

8-OhdG	8-Hydroxydeoxyguanosine
BPDE	Benzo(a)pyrene diolepoxide
DNA	Deoxyribonucleic acid
GSH	Glutathione
GSTA	A isoform of the glutathione S-transferase
GSTP	P isoform of the glutathione S-transferase
LDL	Low Density Lipoprotein
MDA	Malondialdehyde
ROS	Reactive oxygen species
SOD	Super-oxide dismutase
TBARS	Thiobarbituric acid reactive substances