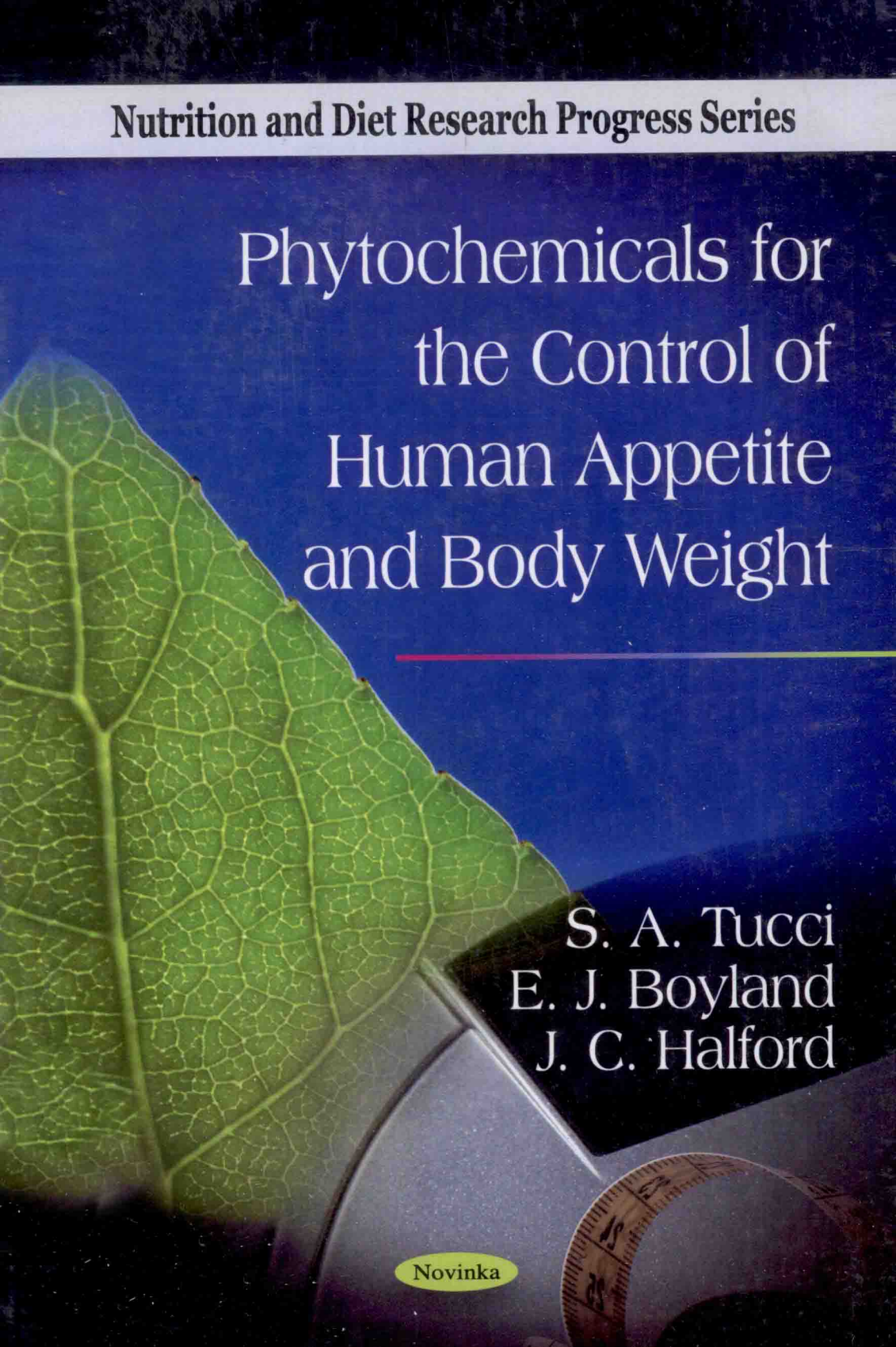
Nutrition and Diet Research Progress Series

Phytochemicals for the Control of Human Appetite and Body Weight



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PHYTOCHEMICALS FOR THE CONTROL OF HUMAN APPETITE AND BODY WEIGHT

S.A. TUCCI, E.J. BOYLAND AND J.C. HALFORD

常州大学山书馆 藏书章

Nova Science Publishers, Inc.
New York

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LIBRARY OF CONGRESS CATALOGING-IN-PUBLICATION DATA

Available upon Request
ISBN: 978-1-61668-676-5

Published by Nova Science Publishers, Inc. † New York

PREFACE

The regulation of energy balance and body weight is under the influence of complex neural, metabolic and genetic interactions. Despite this, obesity is now a global epidemic associated with significant morbidity and mortality in adults and ill health in children. Thus the effective management of obesity has become an important clinical issue. To date there are very few approaches to weight management effective in the long term. This contrasts with disorders such as anorexia and bulimia nervosa which also appear in part to be phenomena of the modern environment and equally difficult to treat. This book will focus on the mechanisms of body weight regulation and the effect of plants or plant extracts (phytochemicals) on these mechanisms. As phytochemicals are often not single compounds but rather a mixture of different unrelated molecules, their mechanism of action usually targets several systems. In addition, since some cellular receptors tend to be widely distributed, sometimes a single molecule can have a widespread effect. We will attempt to describe the main phytochemicals that have been suggested to affect the homeostatic mechanisms that regulate, and some non-homeostatic system that influence, body weight. The in vitro, pre-clinical and clinical data will be summarised and scientific evidence will be reviewed.

CONTENTS

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ABBREVIATIONS

2-AG	2-arachodonoyl glycerol
5-HT	Serotonin, 5-Hydroxytryptamine
α-MSH	α- Melanocyte-stimulating hormone
Δ^9-THC	Δ^9-Tetrahydrocannabinol
A	Adrenaline
ARC	Arcuate nucleus
ATP	Adenosine-triphosphate
BMI	Body mass index
CART	Cocaine-and-amphetamine-regulated transcript
CCK	Cholecystokinin
CNS	Central nervous system
COMT	Catechol-o-methyl transferase
CPT	Carnitine palmitoyltransferase
CRH	Corticotropin releasing hormone
DA	Dopamine
DMN	Dorsomedial nucleus
EC	Epicatechin
ECG	Epicatechin gallate
EE	Energy expenditure
EGC	Epigallocatechin
EGCG	Epigallocatechin gallate
EI	Energy intake
FFA	Free fatty acids
GALP	Galanin-like peptide
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1

GCBE	Green coffee bean extract
GTE	Green tea extract
HCA	(−)- hydroxycitric acid
LH	Lateral hypothalamus
NA	Noradrenaline
NPY	Neuropeptide Y
PFC	Prefrontal cortex
PVN	Paraventricular nucleus
PYY	Peptide YY
TG	Triglycerides
SNS	Sympathetic nervous system
UCP-1	Uncoupling protein 1
VTA	Ventral tegmental area

Chapter 1

INTRODUCTION

Ingestive behaviour in humans is influenced by a complex set of innate and cognate processes modulated by culture and the external environment [1]. From the physiological point of view, an appropriate supply of micro- and macronutrients is required for life. This has lead to the evolution of strong biological mechanisms that defend food supply just as they do for other biological needs [2]. Eating more food than necessary for daily energy expenditure (EE) in times of food plenty increased chances of survival during subsequent periods of famine. As a consequence, most vertebrates developed the ability to store a considerable amount of energy and some micronutrients for later use. However, this ability has now become one of the biggest health risks for many human populations [1]. The uninterrupted supply of cheap energy-dense foods together with an increasingly sedentary lifestyle has led to obesity in a large segment of the human population.

Weight gain and obesity are a result of positive energy balance due to a long-term mismatch between energy intake (EI) and EE. Obesity constitutes a major global health problem as it is a risk factor for several chronic disorders such as diabetes, hyperlipidemia, hypertension, cardiovascular disease, osteoarthritis and some forms of cancer [3]. The most widely advocated means of resolving the obesity epidemic are changes in lifestyle, dieting and exercise. Nevertheless, while losing weight in the short term is achievable, data suggest that maintaining reduced body weight over the long term has proven to be exceedingly difficult for most people [4, 5]. At least part of the reason behind the difficulty of maintaining a reduced body weight is the body's ability to activate adaptive mechanisms that act to minimize weight loss such as an increase in both the motivation to find food and the size of individual meals

[6] which is accompanied by a decrease in metabolic rate [7] that lasts until energy stores are replenished. Therefore one rationale for pharmacotherapy and alternative approaches has been to sustain weight loss behaviour by dampening these compensatory mechanisms. Pharmacologic agents designed to suppress hunger have promoted weight loss, but were often accompanied by unacceptable side effects. For instance, amphetamine-based anorexigens have been effective in some patients, but in some also produced a variety of undesirable effects of mood and behavioural expression. These agents are also prone to abuse and may have the potential to produce chemical dependency [8].

Nonetheless, over the last 20 years, many drugs lacking amphetamine-like side effects have been successfully employed. Some of these agents were the beta-phenethylamine derivatives which had lower abuse potential and proved to be useful in some individuals. Nevertheless, side effects such as insomnia, anxiety and irritability precluded its widespread use [8]. The limited efficacy of beta-phenethylamine derivatives prompted research into a new class of agents, ones acting on serotonergic neurotransmission. Fenfluramine hydrochloride (Pondimin®) and then dexfenfluramine hydrochloride (Redux®, Adifax®) although widely effective, they were implicated in the development of cardiac valvulopathy [9] and in consequence withdrawn from the market. In 1997, sibutramine (Reductil®, Meridia®), a serotonin (5-hydroxytryptamine; 5 -HT)-and noradrenaline (NA)-reuptake inhibitor was introduced into the market. Sibutramine possesses effective weight loss and low weight maintenance properties. However, its use has been associated with several psychiatric [10-14] and possible cardiovascular disorders related to transient increases in blood pressure and heart rate [15]. This may preclude its use in patients with particular psychiatric conditions (although the drug was originally developed as an anti-depressant [16]) and more importantly its effects on patients with cardiovascular conditions is still under investigation [17, 18]. Since such conditions are usually concomitant with obesity, potentially a proportion of obese patients may not be suitable for sibutramine therapy [19]. Orlistat (Xenical®), an intestinal lipase inhibitor, hinders the breakdown of fat in the intestines and as a consequence this undigested fat is not absorbed but excreted [20]. The presence of undigested fat in the bowels causes side effects (such as diarrhoea, abdominal pain, oily stools and faecal spotting) that limit use of orlistat [21]. Additionally, chronic gastrointestinal (GI) ailments like irritable bowel syndrome are clear contraindications for its use. These issues, along with the potential for abuse of this drug as a purgative, and possible deficiencies in fat soluble vitamins associated with use,

have caused some concern. Nonetheless, a half dose of orlistat (Alli® , 60mg rather than 120 mg three times daily) has been approved in Australasia, USA and EU for over-the-counter use [21]. More recently, an approach that attempts to manipulate the mechanisms involved in the motivation to eat and the rewarding or hedonic properties of food is emerging. The drugs recently under investigation target the cannabinoid system which is thought to modulate food intake and energy balance.

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Chapter 2

MECHANISMS THAT REGULATE BODY WEIGHT

SIGNALS OF ENERGY INTAKE AND FAT STORAGE

One of the major determinants of the survival of higher organisms including mammals is the ability to maintain a stable body weight. Body weight regulation mainly concerns adipose tissue since protein and carbohydrate stores in adults only vary a relatively small amount. Therefore, a chronic imbalance between EI and EE results in changes in adipose tissue mass [22]. Body weight, similarly to other physiological processes, is regulated by a feedback mechanism that integrates peripheral and central signals in order to generate an adequate response.

The afferent limb of the feedback mechanism of body weight regulation consists of substances that reflect the metabolic status of the organism. For instance, adipose tissue produces leptin. Leptin is the product of the *ob* gene [23] and correlates positively with the amount of adiposity [24]. Leptin levels are monitored by the hypothalamus, where the binding of leptin to its receptor alters the expression of several genes that encode for neuropeptides involved in modulating food intake and EE [25]. As with leptin, circulating levels of insulin are also proportional to adiposity [26]. Adiponectin is another protein produced by adipose tissue; similarly to leptin, its secretion depends on fat store status but in contrast to leptin adiponectin plays a fundamental role in promoting lipolysis. Adiponectin plasma concentration is inversely correlated with adiposity and increases after food restriction [27]. Ghrelin is the first described GI hormone that stimulates food intake [28], it is released by the

stomach and the intestine in the fasting state and situations of anticipated eating. It is suspected that the high levels of ghrelin generated by low calorie diets could be responsible for rebound weight gain [29, 30]. Cholecystokinin (CCK) is synthesised by endocrine cells in the duodenum and jejunum, and it was the first gut hormone shown to dose-dependently decrease food intake in several species, including humans [31-33]. CCK is one of the earliest short-term satiety signals. Similarly to CCK, peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) also have satiating properties, being released by the ileum and colon in response to the presence of lipids and carbohydrates.

CENTRAL CONTROL OF ENERGY BALANCE

The detection and integration of the above mentioned orexigenic and anorexigenic signals (reviewed in [34]) occurs in the hypothalamus. Due to the absence of a blood-brain barrier, the arcuate nucleus (ARC) of the hypothalamus is considered to play a key integrative role between the initial afferent signals from the periphery and the central nervous system (CNS) responses. In addition to expressing receptors for the above mentioned peripheral signals [35, 36], ARC neurones also sense blood glucose levels [37]. The ARC has neuronal subpopulations that produce orexigenic (neuropeptide Y (NPY) and agouti-related peptide (AgRP)) as well as anorexigenic peptides (α-melanocyte-stimulating hormone (α-MSH), galanin-like peptide (GALP), and cocaine-and-amphetamine-regulated transcript (CART)). The ARC neurones project to "second-order" neurones implicated in the control of feeding such as the paraventricular nucleus of the hypothalamus (PVN), the dorsomedial hypothalamic nucleus (DMN), and the lateral hypothalamic area (LH) [38, 39]. When adiposity signals reach the ARC, anorexigenic peptides are released which activate a catabolic circuit. In contrast, when adiposity signal concentrations in the brain are low, orexigenic peptides are released activating an anabolic pathway [40].

Initially the LH was identified as a 'hunger centre' because lesions in this area produced temporary aphagia, adipsia, and reductions in body weight. Two sets of neurones that contain either orexin [41] or melanin concentrating hormone [42], both potent stimulators of food intake, have been identified in this area. Both types of neurones have a wide projection field to key cortical, limbic, and basal forebrain areas [43, 44]. The DMN receives inputs from cells in the ARC and from brainstem centres. Lesions restricted to the DMH typically result in hypophagia. The PVN integrates signals of different brain

regions and triggers endocrine (through corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone), and autonomic responses .

Another system, the endocannabinoid system, has recently been implicated in the regulation of appetite. The role of this system in feeding regulation is supported by reports indicating that endocannabinoid systems are essential to suckling and growth in neonates [45], and are involved in feeding responses across the phylogenetic scale [46]. Brain endocannabinoid levels have been reported to be elevated in fasted rats [47], and administration of cannabinoid receptor agonists increase food intake [48, 49] while antagonists decrease it [50]. Overall, current data indicate that tonic endocannabinoid release may be crucial to the normal expression of feeding and possibly to the long-term regulation of body weight. In addition, the biosynthesis of the endocannabinoids anandamide and 2-arachodonoyl glycerol (2-AG) appears to be regulated by leptin [51]. Thus, leptin administration suppresses hypothalamic endocannabinoid levels in normal rats; while genetically obese, chronically hyperphagic rodents express elevated, leptin-reversible, hypothalamic anandamide or 2-AG levels [52].

In addition to receiving a fairly complex input on the individual's metabolic status, the hypothalamus integrates the motivation and emotion-related features of feeding behaviour (via direct interactions with medial prefrontal (PFC) and cingulate cortex, basal forebrain and medial septal nuclei) with more fundamental aspects of appetitive and aversive responses (via interaction with nucleus accumbens (NAc), amygdala, ventral tegmental area (VTA), substantia nigra and raphe) [53-58]. After processing this information it sends its output mainly through three pathways: the endocrine system (pituitary gland), the sympathetic nervous system (SNS), and motor expression (promotion or inhibition of food intake) [59, 60]. These pathways constitute the efferent loop in the body weight control system. The endocrine system and SNS act mainly to control EE.

SYSTEMS IMPLICATED IN ENERGY EXPENDITURE

EE is the second aspect of energy balance (the first being food intake). Total EE is the sum of resting EE, the thermic effect of food, and EE related to activity (for review, see [61, 62]). Resting EE or basal metabolic rate is the energy used for cell metabolism to keep cells alive. The intrinsic inefficiency of these cellular events generates a certain amount of heat known as "obligatory thermogenesis". In humans, resting EE is relatively fixed, it

primarily reflects body weight and composition, and is generally the largest component of total energy expenditure (65–75%) [63]. In addition, warm-blooded animals need to generate additional heat to reach the optimal core body temperature, also known as ''adaptive thermogenesis.'' [64]. Since energy consumption during thermogenesis can involve oxidation of lipid fuel molecules, regulation of thermogenesis in response to metabolic signals can also contribute to energy balance and regulation of body adipose stores [65].

Food intake is associated with stimulation of EE, also known as diet-induced thermogenesis or the thermic effect of food. The magnitude of the thermic effect is 5 to 10% of the caloric content of ingested carbohydrates, 0 to 3% of that for lipids and 20 to 30% of that for proteins and is, in a situation of energy balance, approximately 10% of the daily energy intake [66]. This energy is consumed during intestinal absorption of nutrients, the initial steps of their metabolism in the body and their storage. In addition, when food is ingested, homeostatic mechanisms need to be activated in order to digest, absorb, distribute and store the nutrients as quickly as possible. The SNS plays a crucial role in this response, since it regulates postprandial blood flow distribution, blood pressure and thermogenic responses to a meal [67]. The SNS role in postprandial thermogenesis depends on the size and macronutrient composition of the meal and is most evident after high carbohydrate meals [68]. Obesity leads to increased levels of sympathetic activity, and overconsumption and high carbohydrate diets may lead to gradual downregulation of the β-adrenoceptor-mediated thermogenic and metabolic responses, which may be involved in the development of obesity [69-71].

In lean and obese adults weight loss significantly reduces EE beyond levels predicted solely on the basis of changes in weight and body composition [72]. However, there is little evidence of energy wastage in periods of overnutrition [73, 74]. Small increases in EE, if not accompanied by an equivalent increase in EI, would induce a slight negative energy balance and thereby influence body weight regulation in the long term. Thus, direct stimulation of EE may be used as a strategy to improve body weight loss and prevent (re)gain. It is well established that increasing EE at the same time as decreasing EI is more likely to result in significant weight loss and more importantly, weight loss maintenance.

Chapter 3

PHYTOCHEMICALS AND WEIGHT CONTROL

When considering the mechanisms responsible for body weight maintenance it can be concluded that it could be achieved through manipulation of the following: EE (mainly thermogenesis), appetite suppression/satiety enhancement, and fat and glucose absorption blocking. The phytochemicals described below can alter either one single component but more frequently they exert their effect through a combination of modes of action.

Foods are an obvious source of phytochemicals and many may possess specific ingredients that alter appetite beyond the effects expected by normal nutrient loads. Additionally, many therapeutic herbs and nutrients have far fewer side effects and may provide an alternative treatment or could be used to enhance the effect of prescription medications. In this chapter, recent *in vitro*, animal and human studies on the effects of phytochemicals in body weight are examined and summarised. Although most phytochemicals that affect body weight regulation have a complex mechanism of action, for the purpose of this book they will be grouped according to their main effect (increase or decrease body weight) and the site of main mechanism of action (CNS, peripheral or both).

PHYTOCHEMICALS THAT DECREASE BODY WEIGHT MAINLY THROUGH A PERIPHERAL MECHANISM

Korean Pine Nut Oil

Nuts, in their various forms, are widely consumed across the globe, and have recently been linked with the positive health benefits of the Mediterranean diet [75]. Nut consumption is purported to have many health benefits, particularly some protective effects against cardiovascular disease [76, 77] , and it has also been suggested that nuts have satiety enhancing ingredients as there is some epidemiological evidence linking nut consumption inversely with body weight [77]. These properties may relate to their general nutritional content such fibre and protein and/or specific oils. Oils are major constituents of nuts, constituting as much as 60% of the total weight in pine nuts.

Korean pine nut oil (Pinnothin®) is obtained by natural pressing of Korean pine nuts (*P. koraiensis*) and it contains triglycerides (TG) and more than 92% poly- and mono-unsaturated fatty acids (PUFAs and MUFAs) like pinolenic acid (C18:3), linoleic acid (C18:2) and oleic acid (C18:1) [78]. Korean Pine nut oil is claimed to be unique in that it contains approximately 15% pinolenic acid (C18:3). Previous studies on Korean pine nut oil have shown beneficial effects on lipoprotein metabolism and immune function [79, 80]. *In vitro*, Korean pine nut free fatty acids (FFA) have the ability to significantly increase the release of satiety hormones such as CCK from the murine neuroendocrine tumour cell line STC-1 [81]. *In vivo*, fat digestion leads to formation of monoglycerides and fatty acids. These products of fat digestion lead to an increase in CCK, GLP-1 and PYY secretion. However, only fatty acids with chain lengths $\geq$ C12 are capable of triggering the release of CCK and GLP-1 [82, 83]. Moreover, CCK delays gastric emptying and produces a subsequent increased feeling of satiety and a decreased appetite. In terms of inducing satiety hormone secretion, long chain fatty acids are more effective than medium chain fatty acids, and poly-unsaturated fatty acids are more effective than mono-unsaturated fatty acids [84, 85].

The fact that Korean pine nut FFA had the ability to significantly increase satiety hormones *in vitro* lead to the examination of this potential effect in human participants. Administration of pine nut FFA to overweight postmenopausal women produced a significant increase of CCK-8 and GLP-1

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