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Review

Possible anti-obesity therapeutics from nature – A review

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ABSTRACT

Obesity is associated with many diseases, particularly diabetes, hypertension, osteoarthritis, and heart disease. The obesity incidence has increased at an alarming rate in recent years, becoming a worldwide health problem, with incalculable social costs. Two different obesity-treatment drugs are currently on the market: orlistat, which reduces intestinal fat absorption via inhibiting pancreatic lipase; and sibutramine, an anorectic or appetite suppressant. Both drugs have hazardous side-effects, including increased blood pressure, dry mouth, constipation, headache, and insomnia. For this reason, a wide variety of natural materials have been explored for their obesity treatment potential. These are mainly complex products having several components with different chemical and pharmacological features. This review aimed to survey the literature covering natural products with anti-obesity activity and to review the scientific data, including experimental methodologies, active components, and mechanisms of action against obesity.

Contents

1. Introduction

On a global scale, obesity has reached epidemic proportions and is a major contributor to the global burden of chronic disease and disability. Currently, more than one billion adults worldwide are overweight and at least 300 million of them are clinically obese (WHO, 2009).

Two different types of obesity-treatment drugs are currently available on the market (Chaput et al., 2007). One of these is orlistat (Xenical), which reduces intestinal fat absorption through inhibition of pancreatic lipase (Ballinger and Peikin, 2002; Drew et al., 2007; Hutton and Fergusson, 2004; Thurairajah et al., 2005). The other is sibutramine (Reductil), which is an anorectic,

Abbreviations: ACC, acetyl-CoA carboxylase; AMPK, adenosine 5′-monophosphate-activated protein kinase; BAT, brown adipocyte tissue; C/EBP, CCAAT enhancer binding protein; CNS, central nervous system; CPT, carnitine palmitoyltransferase-1; DHA, docosahexaenoic acid; ECG, (−)-epicathin-3-gallate; EGG, (−)-epigallocatechin; EGCG, (−)-epigallocatechin-3-gallate; EPA, eicosapentaenoic acid; ERK, extracellular signal-regulated kinases; FA, fatty acid; GLUT, glucose transporter; GPDH, glycerol-3-phosphate dehydrogenase; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HFD, high fat diet; 5-HT, 5-hydroxytryptamine; IC_{50}, the half maximal inhibitory concentration (with triolein as a lipase substrate); MAPK, mitogen-activated protein kinase; MCH, melanin-concentrating hormone; PPAR, peroxisome-proliferator activated receptor; PUFA, polyunsaturated fatty acids; RQ, respiratory quotient; TG, triglyceride; TNF, tumor necrosis factor; UCP, uncoupling protein; WAT, white adipocyte tissue.

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or appetite suppressant (Lean, 2001; Poston and Foreyt, 2004; Tziomalos et al., 2009). Both drugs have side-effects, including increased blood pressure, dry mouth, constipation, headache, and insomnia (de Simone and D'Addeo, 2008; Karamadoukis et al., 2009; Slovacek et al., 2008; Thurairajah et al., 2005). A number of anti-obesity drugs are currently undergoing clinical development, including centrally-acting drugs (e.g. radafaxine and oleoyl-estrone), drugs targeting peripheral episodic satiety signals (e.g. rimonabant and APD356), drugs blocking fat absorption (e.g. cetilistat and AOD9604), and human growth hormone fragments (Halford, 2006; Melnikova and Wages, 2006).

At present, because of dissatisfaction with high costs and potentially hazardous side-effects, the potential of natural products for treating obesity is under exploration, and this may be an excellent alternative strategy for developing future effective, safe anti-obesity drugs (Mayer et al., 2009; Nakayama et al., 2007; Park et al., 2005). A variety of natural products, including crude extracts and isolated compounds from plants, can induce body weight reduction and prevent diet-induced obesity. Therefore, they have been widely used in treating obesity (Han et al., 2005a; Moro and Basile, 2000; Rayalam et al., 2008).

A wealth of information indicates numerous bioactive components from nature are potentially useful in obesity treatments. A good example of such is the polyphenols. These show strong anti-obesity activity and include apigenin, genistein, and the catechins (Rayalam et al., 2008; Thielecke and Boschmann, 2009; Wolfram et al., 2006).

To date, despite the appearance of several excellent reviews of anti-obesity agents in the literature, no reviews have focused on summarizing real, natural-product data on anti-obesity activity, active compound types, and mechanisms of action. In 2000, Moro and Basile reviewed the use of certain well-known medicinal plants that had claimed to be useful in treating obesity (Moro and Basile, 2000). Five years later, Han et al., 2005a reviewed the anti-obesity effects of natural products from more diverse sources. More recently, the review of anti-obesity phytochemicals by Rayalam et al. (2008) focused on adipocyte life cycle regulation. However, these reviews do not provide updates from the literature regarding various natural products that have anti-obesity effects.

Therefore, in this review, we surveyed natural products with anti-obesity potential and reviewed the scientific data, including experimental methodologies, active components, and mechanisms of action against obesity. A growing body of evidence indicates that natural products having anti-obesity effects can be arranged into five categories based on their distinct mechanisms; they produce (1) decreased lipid absorption, (2) decreased energy intake, (3) increased energy expenditure, (4) decreased pre-adipocyte differentiation and proliferation, or (5) decreased lipogenesis and increased lipolysis. Therefore, in this review, we addressed naturally-occurring compounds possessing anti-obesity activity addressed by categorizing them per these mechanisms.

2. Natural materials for treatment of obesity

2.1. Lipase inhibitory effect

Among treatments for obesity, one of the most promising strategies in the effort to reduce energy intake through gastrointestinal mechanisms, without altering the central mechanisms, is the development of nutrient digestion and absorption inhibitors (Birari and Bhutani, 2007). Dietary fat is not directly absorbed by the intestine unless the fat has been subjected to the action of pancreatic lipase. Therefore, pancreatic lipase is one of the most widely studied mechanisms for determining natural products' potential efficacy as anti-obesity agents (Birari and Bhutani, 2007).

Pancreatic lipase is a key enzyme in dietary triacylglycerol absorption, hydrolyzing triacylglycerols to monoacylglycerols and fatty acids. Only a few substances interact directly with the lipases themselves. One example is tetrahydrolipstatin (orlistat), a derivative of the naturally-occurring lipase inhibitor produced from *Streptomyces toxytricini* (Ballinger and Peikin, 2002). Orlistat's lipase inhibition mechanism acts through a covalent bond to the lipase's active site serine (Hadváry et al., 1988, 1991; Tsujita et al., 2006). Although this pancreatic lipase inhibitor is clinically approved for obesity treatment, orlistat has certain unpleasant gastrointestinal side-effects (Karamadoukis et al., 2009; Thurairajah et al., 2005). These side-effects result from orlistat's mode of action and include oily spotting, liquid stools, fecal urgency or incontinence, flatulence, and abdominal cramping (Chaput et al., 2007). Therefore, researchers are screening novel inhibitors, derived from plants or other natural sources, that lack some of these unpleasant side-effects (Birari and Bhutani, 2007).

Natural products provide a vast pool of pancreatic lipase inhibitors with potential for being developed into clinical products. Birari and Bhutani, 2007 reviewed various extracts and secondary metabolites, derived from plants and microorganisms, that have pancreatic lipase inhibitory activity. Drug development programs should focus on these extracts and metabolites.

A wide variety of plants possess pancreatic lipase inhibitory effects, including *Panax japonicus* (Han et al., 2005b), *Platycodi radix* (Han et al., 2000), *Salacia reticulata* (Kishino et al., 2006), *Nelumbo nucifera* (Ono et al., 2006), and so on (see Table 1 for details). These pancreatic lipase inhibitory phytochemicals include mainly saponins, polyphenols, flavonoids, and caffeine (Kim and Kang, 2005; Han et al., 2006; Moreno et al., 2006; Shimoda et al., 2006).

Several carbohydrates also possess pancreatic lipase inhibitory effects (Takao et al., 2006). For example, when researchers fed experimental animals a high-fat diet containing 7–15% chitin/chitosan, fat excretion in the feces increased, resulting in reduced body weights (Han et al., 2005a). However, the effects these carbohydrates have on body weight reduction in animals and humans are controversial (Bondiolotti et al., 2007; Gades and Stern, 2003, 2005; Gallaher et al., 2002; Han et al., 1999a; Hayashi and Ito, 2002; Ho et al., 2001; Kaats et al., 2006; Sumiyoshi and Kimura, 2006). We recently found a distinct body weight reduction in *ob/ob* mice fed on chitosan oligosaccharides; proteome analysis of mouse plasma before and after these treatments suggested chitosan oligosaccharide's molecular actions (Kumar et al., 2009). The expression of many genes is altered significantly during the anti-obesity effect, in response to the chitosan oligosaccharide in the diet (Kumar et al., 2009).

Many metabolites from microorganisms, including lipstatin from *Streptomyces toxytricini* (Weibel et al., 1987), panclicins from *Streptomyces* sp. NR0619 (Mutoh et al., 1994; Yoshinari et al., 1994), valilactone and ebelactones from *Streptomyces albolongus* (Kitahara et al., 1987; Umezawa et al., 1980), esterastin from *Streptomyces lavendulae* (Umezawa et al., 1978), caulerpenyne from *Caulerpa taxifolia* (Tomoda et al., 2002), vibralactone from *Boreostereum virans* (Liu et al., 2006), and percyquinin from *Basidiomycete stereum complicatum* (Bitou et al., 1999) also possess pancreatic lipase inhibitory activity. Moreover, certain fruiting bodies or mycelia of macrofungi reportedly possess lipase inhibitory activity (Ahn et al., 2007b; Slanc et al., 2004).

Some of the most widely-studied materials among the many natural sources of pancreatic lipase inhibitors are the different types of tea (e.g. green, oolong, and black tea). A significantly different type of polyphenols (e.g. L-epicatechin, ECG, EGG, and EGCG), isolated from tea leaves, showed strong inhibitory activity against pancreatic lipase (Han et al., 1999b; Lin and Lin-Shiau, 2006; Nakai et al., 2005; Thielecke and Boschmann, 2009). These polyphenols require galloyl moieties within their chemical