International Research Journal of Medical Sciences _____ ISSN 2320 –7353
Vol. **1(9),** 15-26, October **(2013)** *Int. Res. J. Medical Sci.*

Review Paper

Therapeutic Role of Phytomedicines on Obesity: Importance of Herbal Pancreatic lipase Inhibitors

Singh Sukhdev* and Kanwar Shamsher Singh
Department of Biotechnology, Himachal Pradesh University, Summer Hill, Shimla-171 005, INDIA

Available online at: www.isca.in, www.isca.me
Received 7th October 2013, revised 13th October 2013, accepted 25th October 2013

Abstract

Obesity has been declared one of the major threats to human health in 21st century. It has become the center of much clinical attention and especially clinical laboratories, whose aim is to reduce this new world syndrome. Dietary fat is associated with well known diseases like diabetes, hypertension and cardio-vascular diseases. Certain long-term medications like use of insulin, sulfonylureas, thiazolidinediones, atypical antipsycotics, antidepressant, steroids, some anticonvulsants (phenytoin and valproate), pizotifen and some forms of hormonal contraception may also cause weight gain or changes in body composition. Retardation of nutrient absorption and digestion may be used as an approach to manage obesity and related diseases. Orlistat is the only approved drug for long-term use and widely accepted also. However, some side effects and complications are also related with this medication. Currently, plant based natural products as anti-obesity therapeutics is largely unexplored and such products may be safer and effective alternative(s) for this ever increasing pandemic. Anti-nutritional factors (ANF) are natural compounds which act to retard nutrient(s) uptake. Phyto-chemicals like kievitone and visoltricine are useful in pharmacological treatments. Phyto-chemicals like flavonoides, saponins, alkaloids and many others are reported as biologically active molecules. Plants may prove to be an alternative source(s) of a variety of anti-lipolytic therapeutic molecule(s) that can either inhibit the pancreatic lipase or the uptake/absorption of fat(s) or both. In this review we emphasize the potential role of these bioactive compounds as pancreatic lipase (PL) inhibitory molecules. Moreover, medicinal plants are promising sources for isolation, identification and characterization of bioactive compounds for developing effective anti-obesetic agents.

Keywords: Obesity, Orlistat, pancreatic lipase inhibitors and phytochemical(s).

Introduction

Obesity, the 'New World Syndrome' has been declared a global epidemic by WHO[1,2] and is now being recognized as a major health concern especially in new world countries. There are over 400 million clinically obese and 1.6 billion overweight adults according to a WHO survey[3,4]. In developed countries like USA[5], Australia and Canada[6,7] it is increasing at a faster rate. In United States, obesity has been assumed to be an important cause of human deaths[8]. One in three Americans are obese. In the European Union, half population of adults and approximate 20% of school-age children are reported as overweight. In England over a quarter of adults (26%) were reported as obese in 2010[9]. A statistical study report that in US 35% of adults and almost 17% of youth were obese in the year 2009-10[10]. The Indians are also reported for obesity and their consequences[11]. There is a constant rise in obesity related deaths each year. Major health consequences associated with overweight and obesity are dyslipidemia, coronary artery disease, type-2 diabetes, reproductive and gastrointestinal cancers, sleep apnea, stroke, fatty liver and osteoarthritis[12]. Recently, it has been found to promote prostate cancer, too[13]. Obese patients may lower the risk of cardiovascular diseases and type-2 diabetes by reducing only 5-10% weight[14-16]. Medication is also available, as therapeutic compounds that can block/ inhibit fat digestion[17]. Orlistat which is a saturated derivative of Lipstatin[18] lowers the body weight when taken under suitable dietary advice[19,20]. This drug has also been shown to improve OGT (oral glucose tolerance)[21].

Natural compounds from plants and microbes can be developed as anti-obesity clinical products[22]. Retardation of nutrient absorption and digestion may be used as an approach to manage obesity and related diseases. For example, valoneaic acid dilactone from banaba[23], chestnut astringent skin extract[24], α-amylase inhibitor from white beans[25] and acarbose[26] showed clinical effects against diabetes and cardio-metabolic disorders. Marine algae[27], fungi[28] and some plants have been screened for anti-lipase activity[29].

Imbalance between energy intake and energy expenditure leads to over-weight and Obesity[30]. High intake of dietary fat, overeating and reduced physical activity together lead to obesity[31] that are main causes of prevalence of obesity in westernized societies. Normally, man and woman have 18-23% and 25-30% of body fat in average. Women with over 30% and men with over 25% body fat are considered obese. Overweight and obesity are determined by using weight and height to

calculate a number called the 'Body Mass Index' (BMI). The formula for calculating BMI was given by a Belgian scientist Adolphe Quetelet in 1830 to assess the body fat. BMI equals a person's weight in kilograms (kg) divided by his/ her height in meters (m) squared. But recently a modified Quetelet's BMI formula that has been proposed and it is gaining good acceptance[32].

Quetelet's BMI= Weight (kg)/ Height (m^2) = 703 X weight (lb)/ height (in^2)
New formula BMI= 1.3 X Weight (kg)/ Height ($m^{2.5}$) = 5734 X weight (lb)/ height ($in^{2.5}$)

An adult is considered overweight if he/ she has a BMI between 25 and 29.9 and is considered obese if BMI of 30 or higher (table 1).

Table-1
Grades of obesity according to BMI

BMI	Criteria
Below 18.5	Under weight
18.5 to 24.9	Healthy weight
25 to 29.9	Overweight
30 or higher	Obese

In some cases, such as athletes, may be identified as overweight according to BMI even though they do not have excess body fat. So BMI calculation does not take into account the muscular mass (*i.e.* heavy weight lifters) or the stage of development (*i.e.* when our body is still developing). A few other methods that may be useful to diagnose the level/ grade of obesity include; i. Waist circumference, saggital diameter and waist-to-hip ratio: 102 cm (40 inches) for a man and 88 cm (35 inches) for a woman is currently recommended upper limit for waist circumference in the United States. Waist-to-hip ratio greater than 1 in men or greater than 0.85 in women is considered obese[9]. ii. Skin fold caliper: This test measures fat beneath the skin, but cannot measure fat accumulated inside the abdomen[33]. iii. Water displacement test: Determining how well we float provides an estimated ratio of fat to body mass[34]. iv. Blood tests: To assess other medical conditions in which body weight increases (like thyroid disorder), some blood tests can also be performed[35,36].

Alimentary obesity makes up most of obesity cases and results when a person consumes more calories than he/ she can burn. Some cases of secondary obesity results in disorders like Cushing's syndrome[37], polycystic ovary syndrome (PCOS)[38] and insulin tumors[39]. Childhood obesity occurs when children and adolescents are above the normal body weight for their age and height. A limited number of cases are primarily due to genetics, medical reasons or psychiatric illness[40].

Sometimes weight excess is also a major feature in some syndromes[41], such as Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome and MOMO syndrome. A few cases are also reported with single point DNA mutation[42]. Some cases like hypothyroidism, Cushing's syndrome and growth hormone deficiency also reported to weight gain[43]. Some long-term medications may also cause weight gain or changes in body composition[44]; these include insulin, sulfonylureas, thiazolidinediones, atypical antipsycotics, antidepressant, steroids, some anticonvulsants (phenytoin and valproate), pizotifen and some forms of hormonal contraception. Some other factors, which also play a role in obesity may include;

Age: At older age body's ability to metabolize food slows down and there is less requirement of calories to maintain body weight. So at age of 40 or after we tend to gain weight[45]. There's some evidence that when an older a woman gives birth, there is a higher child's risk of obesity[45].

Gender: Women tend to be more overweight than men due to difference in resting metabolic rate. Additionally, women tend to gain weight after menopause.

Environmental factors: Environmental factors unknowingly affect our metabolism[46]. We know hormones regulate body weight and many of today's pollutants affect our hormones[47]. For convenience we are living in temperature-controlled rooms/ office[48,49]. Moreover, smoking also reduces weight[50,51].

Psychological factors: Many persons eat in response to boredom, sadness or anger. Too little sleep may also result in gain of body weight[52-54].

Genetic factors: Some of the genetic factors predispose us to obesity[55]. Some reports evidencing fertility of obese people than leaner ones[56]. If obesity has a genetic component[57], the percentage of obese people in the population will increase. Moreover, union of obese spouses also promotes the chances to have obese child in generation[58].

Clinical management of obesity: drugs and surgery

In most cases patients who lose weight, regain the weight in subsequent years suggesting obesity has a high relapse rate making difficulty in treatment. So the treatment has to be a life-long commitment with proper dietary habits and increased physical activities. Pathetically obese patients may lower the risk of cardiovascular diseases and type-2 diabetes by reducing only 5-10% weight. Therapeutic treatment of overweight patients has benn reviewed[59,60]. Leptin, a peptide hormone, was discovered to regulate body weight[61-63]. Details and additional guidance for the medications to treat overweight patients have been published time-to-time[64-71]. Currently, the options of medications available to treat overweight patients are quite limited. Additionally, the side effects of these medications are also major concerns to clinicians, particularly for appetite-suppressant drugs. Fenfluramine[72] was withdrawn from market after reports of cardiac fibrosis and pulmonary hypertension

came into light[73,74]. Phentermine is available only for short-term use. Sibutramine (Meridia) may cause an increase in blood pressure[75].

One medication, Orlistat can lose weight up to 2.9 kg (6.4 lb) in 1 to 4 years. However, some side effects and complications are also related with this medication[76]. This drug blocks the absorption of dietary fat and causes unpleasant side effects like oily stools, diarrhoea, abdominal pain, faecal spotting and some hepatic toxicity effects. Orlistat causes high rates of side-effects on gastrointestinal tract and on kidneys[77]. Another drug Lorcaserin (Belviq) lose weight by 3.1 kg over a year[78]. Combination of phentermine and topiramate has also been approved[79].

Surgery may help patients who are in pathetic condition. Two bariatric surgical procedures: gastric bypass and Lap-Band have proved to be effective for treating obese patients[80]. Gastric bypass surgery causes permanent changes in gastrointestinal tract and its effects cannot be reversed.

Pharmaceutical potential of phyto-chemicals

Plants are in use since several years as traditional and natural pharmaceutical aids[81]. Plant-based medicines cover an important portion in current pharmaceutics that we are using these days[82]. Many phyto-chemical compounds have been discovered till now for pharmaceutical values, and anti-nutrients are one of them[83-85]. Phyto-chemicals like kievitone and visoltricine are useful in pharmacological treatments[86]. Antinutrients can be developed in pharmaceutical principals[87]. Although they elicit deleterious effects on human health[88,89] but they also have been shown to be of pharmaceutical importance[90,91]. Phyto-chemicals like flavonoides, saponins, alkaloids and many others are reported as biologically active molecules (table 2 and 3) and have been identified in many pharmacological studies[91,92]. Saponins[93] play an important role in foam industries[94], beverages industries[95], agriculture[96], antibiotics[97] and in antiviral and antifungal pharmaceutics[98]. They also have been proved for their antitumor potential[99] and particularly saponin(s) like ginseng, quillaja and gypsophila are constituents of some anti-cancerous drugs[100]. They are proved for their cholesterol lowering potential[87,101] and for anti-diabetic[102] and antiulcer[103] effects. Saponins also exhibit promising role(s) in some cardiovascular treatments[104] and as strong anti-inflammatory agents[105]. They are also reported to scavenge ROS[106-108]. Besides potent free radical scavengers[109], flavonoids particularly genistein have been shown as anti-cancerous phyto-molecule[110,111]. Flavonoids[101,112] are also used in food processing industries[113] and they also have insecticidal properties[114]. Tannins[115] are also considered as anti-tumor agents[116], antimicrobial agents[117] and as anti-helmintic agents[118-120]. Condensed tannins are reported to be beneficial in agriculture, in nutrition and health of ruminants[121]. Alkaloids are known as strong anti-inflammatory agents[122]. Protease inhibitors have also been reported for their insecticidal properties[123-125].

Therapeutic interventions to manage obesity using phytomolecules

Phytomolecules may play the key role as an anti-obesetic agent via distinct mechanisms. They may reduce lipid absorption from food, reduce energy intake from diet, enhance energy expenditure by degrading stored fat, decrease pre-adipocyte differentiation and proliferation and boost up the lipolysis of accumulated fat in our body (figure 1). As dietary fat is responsible for adiposity so to develop lipid digestion and absorption inhibitors, pancreatic lipase may be targeted for drug development as it is the key component in fat digestion. To develop novel inhibitors those lack unpleasant side effects, phyto-chemicals and secondary metabolites from plants and microbial sources can be focused for antiobesity medication development programme.

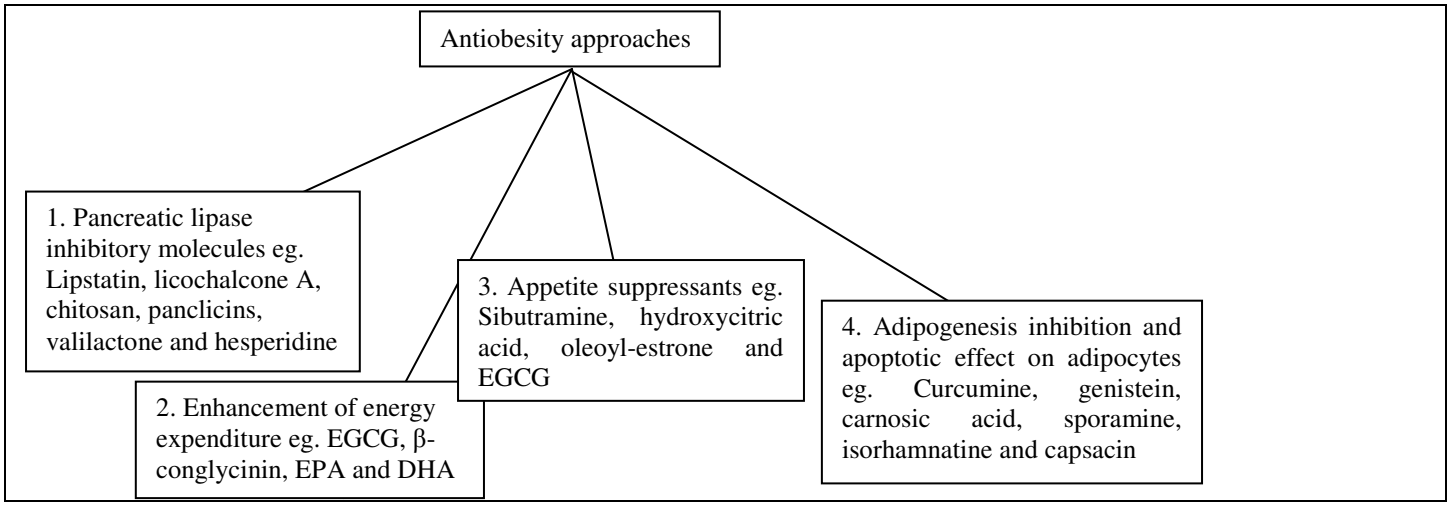

Figure-1
Antiobesetic medication strategies

Many phyto-chemicals and metabolites that possess pancreatic lipase inhibitory actions have been reported (table 2, 3 and 4). Energy intake reduction via appetite suppression also provides an option for obesity treatment[126]. Sibutramine is an appetite suppressant that acts by controlling noradrenaline, serotonine, hydroxytryptamine and dopamine[127]. Some natural appetite suppressants have also been discovered like *Hoodia gordonii*[128], *Garcinia cambosia*[129] and *Cissus quadrangularis*[130]. Some of the herbal remedies also reported lose weight via enhanced energy expenditure like EGCG from green tea[131], *Pinellia turnate*[132] and *Panax ginseng*[133]. Some phyto-chemical compounds like quercetin, esculetin, genistein, resveratrol and capsaicin shown as antiobesity agents act via adipogenesis inhibitors and apoptotic on adipocytes[134].

Anti-obesetic phyto-molecules as pancreatic lipase inhibitors

The main issue, need to be kept in mind before any effective drug widely accepted, is the toxicity of therapeutic and of course it must also not be addictive. In this concern plants may prove to be an alternative source(s) of a variety of anti-lipolytic therapeutic molecule(s) that can either inhibit the pancreatic lipase or the uptake/absorption of fat(s) or both. Phyto-chemicals present in plants offer us the safer natural products that can be developed in the form of therapeutics (table 2). These bioactive compounds can be extracted and purified in many ways[135]. For the pandemic cases these bioactive compounds can be targeted on lipid metabolic pathways. A very large pool of enzymes related to fat digestion has been discovered and can be targeted for development of therapeutics for obesity and related diseases[136].

Table-2
Antiobesetic molecules reported from plants

Source	Family	Antiobesetic agent	Ref. (s)
Oryza sativa	Poaceae	Phenylboronic acid	137
Salvia officinalis	Lamiaceae	Carnosic acid (Diterpene)	138
Platycodon grandiflorus	Campanulaceae	Platycodin D (Saponin)	139-141
Glycyrrhiz auralensis	Fabaceae	Licochalcone A (Polyphenol)	142
Scabiosa tschiliensis	Caprifoliaceae	Prosapogenin (Saponin)	143
Acanthopanax sessiliflorus	Araliaceae	Sessiloside and chiisanoside (Saponins)	144
Panax japonicas	Araliaceae	Chikusetsusaponins (Saponin)	145
Dioscorea nipponica	Dioscoreaceae	Dioscin (Saponin)	146
Aesculus turbinate	Sapindaceae	Escins (Saponin)	147
Cyclocarya paliurus	Juglandaceae	Cyclocariosides (Saponin)	148
Gardenia jasminoids	Rubiaceae	Crocin (Terpene)	149

Pancreatic lipase, a key enzyme, which is responsible for hydrolysis of a majority of dietary fats[150], may be targeted for the concerned obesity pandemic. Like, Orlistat and Cetilistat acts by inhibiting gastro-intestinal and pancreatic lipases but have side effects including greasy stools, and faecal spotting[151]. And also, it needs supplementation of fat soluble vitamins in diet[152]. So in search of safer anti-obesetic therapeutic several efforts have been made and still going on as pancreatic lipase (PL) inhibitory agents. Many bioactive phyto-chemicals have been screened for their anti-obesetic potential (table 3). Some anti-lipolytic metabolites have been discovered from a variety of microbial and other sources (table 4). Many plant extracts[153-159], fungal extracts[160,161] and chemical compounds like polysaccharides[162], ε-polylysine[163], protamines[164], cholestyramine[165] and soya proteins[166] have been shown to possess anti-lipolytic function(s) against pancreatic lipase.

Table-3
Phytochemicals reported to possess *in vitro* and *in vivo* pancreatic lipase inhibition activity.

Source	Phytochemical(s)	Reference(s)
Camellia sinensis	Proanthocyanidins and catechins	167
Cassia mimosoides	Proanthocyanidins	168
Malus domestica	Procyanidins	169
Coffea arabica	Saponins	170, 171
Cyclocarya paliurus	Saponins	148
Dioscorea nipponica	Saponins	146
Eleutherococcus senticosus	Saponins	172, 173
Eleutherococcus sessiliflorus	Saponins	174
Gardenia jasminoides	Saponins	149
Aesculus turbinate	Saponins	147, 175
Kochia scoparia	Saponins	176
Malus domestica	Saponins	169
Panax ginseng	Saponins	177
Panax japonicus	Saponins	145
Platycodi grandiflorum	Saponins	140, 141
Ilex paraguariensis	Polyphenols and saponins	178
Arachis hypogaea	Polyphenols	153, 154
Camellia sinensis	Theasaponins and polyphenols	179, 180
Nelumbo nucifera	Polyphenols	181
Mangifera indica	Polyphenols	153, 154
Cassia nomame	Condensed tannins	168
Salacia reticulata	Polyphenols	182

Table-4
Anti-lipolytic metabolites discovered in algae, bacteria and fungi

Source	Kingdom	Antiobesetic metabolite	Reference(s)
Streptomyces toxytricini	Bacterium	Lipstatin	18
Streptomyces sp. *NR0619*	Bacterium	Panclicins	183, 184
Streptomyces aburaviensis	Bacterium	Ebelactones	185
Boreostereum vibrans	Fungus	Vibralactone	186
Monascus sp.	Fungus	Penicillamine Derivative	187
Caulerpa taxifolia	Algae	Caulerpenyne	27, 188
Streptomyces albolongus	Bacterium	Valilactone	189
Streptomyces lavendulae strain MD4-C1	Bacterium	Esterastin	190]
Stereum complicatum, ST 001837	Fungus	Percyquinin	191
See weeds	Algae	Fucoxanthinol (carotenoid)	192

Conclusion

Complete understanding of metabolites involved in fat metabolism in our body will open the ways to develop the therapeutics to combat obesity. Pancreatic lipase, a key lipolytic enzyme, is a most attractive target for this purpose. In brief, efforts should be made to develop safer medication to counter the gigantic problem of ever increasing obesity. None of the drugs has been established for long time to cure obesity. The only approved drug, Orlistat, has non ignorable side effects. So in search of nontoxic therapeutic, plant based clinical products are a good option. Pancreatic lipase can be targeted for the concerned pandemic. Pancreatic lipase inhibitors form plant sources as anti-obesetic metabolites has been discovered but none of them reached up to clinical level. Hence concerted efforts are required to explore plants as important natural resources for their therapeutic potential, not only for obesity but for other diseases, too.

Acknowledgements

The financial support from Department of Biotechnology, Ministry of Science and Technology, Government of India, New Delhi as well as to the Department of Biotechnology, Himachal Pradesh University, Shimla (India) is thankfully acknowledged.

Abbreviations: ANF: Anti nutritional factors; PL: Pancreatic lipase; WHO: World Health Organisation: USA: United States of America; BMI: Body Mass Index; MOMO: Macrosomia Obesity Macrocephaly Ocular syndrome; DNA: Deoxyribose nucleic acid; EPA: Eicosapentaenoic acis; DHA: Docosahexenoic acid; EGCG: Epigallocatechin gallate; OGT: Oral glucose tolerance; PCOS: Poly cystic overy syndrome.

References

1. Caballero B. The global epidemic of obesity: An overview, *Epidemiol Rev,* **29**, 1-5, **(2007)**

2. Data and statistics [http://who.int/research/en/],**(2012)**

3. Drew B, Dixon A and Dixon J. Obesity management: update on orlistat, *Vasc Health Risk Manag,* **3**, 817-821, **(2007)**

4. The Global Epidemic [http://iaso.org/iotf/obesity/obesity theglobalepidemic/] (**2012)**

5. Sturm R. Increase in morbid obesity in the USA: 2000-2005, *Pub Health* **121**, 492-96, **(2007)**

6. Tjepkema M., Measured obesity-adult obesity in canada: measured height and weight, Ottawa In: Nutrition: Findings from the Canadian Community Health Survey, **(2005)**

7. Howard, Natasha J, Taylor A, Gill T and Chittleborough C. Severe obesity: Investigating the socio-demographics within the extremes of body mass index, *Obes Res Clin Pract,* **2**, 51-59, **(2008)**

8. Mokdad AH, Marks JS, Stroup DF and Gerberding JL. Actual causes of death in the United States, 2000, *JAMA* **291**, 1238-45, **(2004)**

9. Paul E. In: The NHS Information Centre Lifestyles Statistics: Statistics on obesity, physical activity and diet: England. London, **(2012)**

10. Ogden CL, Carroll MD, Kit BK and Flegal K.M., Prevalence of Obesity in the United States 2009-2010. *NCHS Data Brief,* **82,** 1-8, **(2012)**

11. Kalra S and Unnikrishnan AG. Obesity in India: the weight of the nation, *J Med Nutr Nutraceut,* **1**, 37-41, **(2012)**

12. Padwal R, Li SK and Lau DCW. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. *Int J Obes,* **27**, 1437-1446, **(2003)**

13. Ribeiro R**,** Monteiro C**,** Catalan V**,** Hu P**,** Cunha V**,** Rodriguez A**,** Gomez-Ambrosi J**,** Fraga A**,** Principe P**,** Lobato C**,** Lobo F**,** Morais A**,** Silva V**,** Sanches-Magalhaes J**,** Oliveira J**,** Pina F**,** Lopes C**,** Medeiros R and Fruhbeck G. Obesity and prostate cancer: gene expression signature of human per prostatic adipose tissue, *BMC Med*, **10**, 1-41, **(2012)**

14. Goldstein DJ. Beneficial effects of modest weight loss, *Int J Obes Rel Met Dis,* **16**, 397-415, **(1992)**

15. Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, Smith WCS, Jung RT, Campbell MK and Grant AM. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement, *Health Tech Assess* **8**, 1-458, **(2004)**

16. Padwal RS and Majumdar SR. Drug treatments for obesity: orlistat, sibutramine and rimonabant, *Lancet,* **369**, 71-77, **(2007)**

17. Bray G. and Ryan D., Drug treatment of the overweight patient, *Gastroenterol,* **132**, 2239-2252, **(2007)**

18. Weibel EK, Hadvary P, Hochuli E, Kupfer E and Lengsfeld H. Lipstatin, an inhibitor of pancreatic lipase, produced by Streptomyces toxytricini. I. Producing organism, fermentation, isolation and biological activity, *J Antibiot,* **40**, 1081-1085, **(1987)**

19. McClendon K, Riche D and Uwaifo G. Orlistat: current status in clinical therapeutics. *Expert Opin Drug Saf* **8**, 727-744, **(2009)**

20. Viner RM, Hsia Y, Tomsic T and Wong ICK, Efficacy and safety of anti-obesity drugs in children and adolescents: systematic review and meta-analysis, *Obes Revs* **11**, 593-602, **(2010)**

21. Heymsfield SB, Segal KR, Hauptman J., Lucas CP, Boldrin MN and Rissanen A., Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med* **160**, 1321-1326, **(2000)**

22. Birari RB and Bhutani KK. Pancreatic lipase inhibitors from natural sources: unexplored potential. *Drug Discov Today* **12**, 879-889, **(2007)**

23. Hosoyama H, Sugimoto A, Suzuki Y, Sakane I and Kakuda T. Isolation and quantitative analysis of the alpha-amylase inhibitor in Lagerstroemia speciosa (L.) Pers. (Banaba). *Yakugaku Zassi* **123**, 599-605, **(2003)**

24. Tsujita T, Takaku T and Suzuki T. Chestnut astringent skin extract, an alpha-amylase inhibitor, retards carbohydrate absorption in rats and humans. *J Nutr Sci Vitaminol* **54**, 82-88, **(2008)**

25. Tormo MA, Gil-Exojo I, de Tejada AR and Campillo JE. White bean amylase inhibitor administered orally reduces glycaemia in type 2 diabetic rats, *Br J Nutr,* **96**, 539-544, **(2006)**

26. Yamagishi S, Matsui T, Ueda S, Fukami K and Okuda S. Clinical utility of acarbose, an alpha-glucosidase inhibitor in cardiometabolic disorders, *Curr Drug Metab,* **10**, 159-163, **(2009)**

27. Bitou N, Ninomiya M, Tsujita T and Okuda H. Screening of lipase inhibitors from marine algae. *Lipids* **34**, 441-445, **(1999)**

28. Slanc P, Doljak B, Mlinaric A and Strukelj B. Screening of wood damaging fungi and macrofungi for inhibitors of pancreatic lipase. *Phytother Res* **18**, 758-762, **(2004)**

29. Slanc P, Doljak B, Kreft S, Lunder M, Janes D and Strukelj B. Screening of selected food and medicinal plant extracts for pancreatic lipase inhibition. *Phytother Res* **23**, 874-877, **(2009)**

30. Astrup A. The role of dietary fat in the prevention and treatment of obesity. Efficacy and safety of low-fat diets. *Int J Obes* **25**, 46-50, **(2001)**

31. Schrauwen P and Westerterp KR. The role of high-fat diets and physical activity in the regulation of body weight. Br J Nutr 84, 417-427, **(2000)**

32. BMI (Body Mass Index) [people.maths.ox.ac.uk/trefethen/bmi.html]. **(2013)**

33. *International Society for the Advancement of Kinanthropometry, International Standards for Anthropometric Assessment, Australia, **(2001)***

34. Obesity in adults [globalinc.prod.ehc.com]. **(2012)**

35. Defining overweight and obesity [http://www.cdc.gov/obesity/defining.html], Centers for Disease Control & Prevention, **(2012)**

36. The practical guide: Identification, evaluation and treatment of overweight and obesity in adults, Bethesda, MD; 2000. National Institutes of Health, **(2012)**

37. Bujalska IJ, Kumar S and Stewart PM. Does central obesity reflect Cushing's disease of the omentum. *Lancet* **349**, 1210-1213, (1997)

38. Gambineri A, Pelusi C, Vicennati V, Pagotto U and Pasquali R. Obesity and the polycystic ovary syndrome. *Int J Obes* **26**, 883-896, **(2002)**

39. Giovannucci E. Insulin and colon cancer. *Cancer Causes Control* **6**, 164-179, **(1995)**

40. Bleitch S, Cutler D, Murray C and Adams A. Why is the developed world obese? *Annu Rev Public Health* **29**, 273-295, **(2008)**

41. Walley AJ, Asher JE and Froguel P. The genetic contribution to non-syndromic human obesity. *Nat Rev Genet* **10**, 431-442, **(2009)**

42. Farooqi S and O'Rahilly S. Genetics of obesity in humans. *Endocr Rev* **27**, 710-718, **(2006)**

43. Rosen T, Bosaeus I, Tolli J., Lindstedt G and Bengtsson BA. Increased body fat mass and decreased extracellular fluid volume in adults with growth hormone deficiency. *Clin Endocrinol* **38**, 63-71, **(1993)**

44. Haslam DW and James WP. Obesity. *Lancet* **366**, 1197-1209, **(2005)**

45. Keith SW, Redden DT, Katzmarzyk PT, Boggiano MM, Hanlon EC, Benca RM, Ruden D, Pietrobelli A, Barger JL, Fontaine KR, Wang C, Aronne LJ, Wright SM, Baskin M, Dhurandhar NV, Lijoi MC, Grilo CM, DeLuca M, Westfall AO and Allison DB. Putative contributors to the secular increase in obesity: exploring the roads less traveled. *Int J Obes* **30**, 1585-1594, **(2006)**

46. Pollutants linked to reduced height and body mass [http://ec.europa.eu.environment/integration/research/newsalert/pdf/232na4.pdf]. **(2011)**

47. Verhulst SL, Nelen V, Hond ED, Koppen G, Beunckens C, Vael C, Schoeters G and Desager K. Intrauterine Exposure to Environmental Pollutants and Body Mass Index during the First 3 Years of Life. *Env Health Persp* **117**, 122-126, **(2009)**

48. Herman C., Effects of heat on appetite, National Academy Press, Washington DC **(1993)**

49. Westerterp-Plantenga MS, van Marken-Lichtenbelt WD, Cilissen C and Top S. Energy metabolism in women during short exposure to the thermoneutral zone. *Physiol Behav* **75**, 227-235, **(2002)**

50. Flegal KM, Troiano RP, Pamuk ER, Kuczmarski RJ and Campbell SM. The influence of smoking cessation on the prevalence of overweight in the United States. *N Engl J Med* **333**, 1165-1170, **(1995)**

51. McGovern JA and Benowitz NL. Cigarette smoking, nicotine and body weight. *Clin Pharmacol Ther* **90**, 164-168, **(2011)**

52. von Kries R, Toschke AM, Wurmser H, Sauerwald T and Koletzko B. Reduced risk for overweight and obesity in 5- and 6-year old children by duration of sleep: a cross-sectional study. *Int J Obes Relat Metab Disord* **26**, 710-716, **(2002)**

53. Taheri S, Lin L, Austin D, Young T and Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med Epub, **(2004)**

54. Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity. *Analyses of the NHANES* **28**, 1289-1296, **(2005)**

55. Bouchard C. The biological predisposition to obesity: beyond the thrifty genotype scenario. *Int J Obes* **31**,1337-1339, **(2007)**

56. Jensen TK, Andersson AM, Jorgensen N, Andersen AG, Carlsen E, Petersen JH and Skakkebaek NE. Body mass index in relation to semen quality and reproductive hormones among 1,558 Danish men. *Fertil Steril* **82**, 863-870, **(2004)**

57. Diaz J and Taylor EM. Abnormally high nourishment during sensitive periods results in body weight changes across generations. *Obes Res* **6**, 368-374, **(1998)**

58. Weng HH, Bastian LA, Taylor DH, Moser BK and Ostbye T. Number of children associated with obesity in middle-aged women and men: results from the health and retirement study. *J Wom Health* **13**, 85-91, **(2004)**

59. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L and Friedman JM. Positional cloning of the mouse obese gene and its human homolog. *Nature* **372**, 425-432, **(1994)**

60. Colman E. Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. *Ann Intern Med* **143**, 380-385, **(2005)**

61. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK and Friedman JM. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* **269**, 543-546, **(1995)**

62. Maffei M, Fei H, Lee GH, Dani C, Leroy P, Zhang Y, Proenca R, Negrel R, Ailhaud G and Friedman JM. Increased expression in adipocytes of ob RNA in mice with lesions of the hypothalamus and with mutations at the db locus. *Proc Natl Acad Sci* **92**, 6957-6960, **(1995)**

63. Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, Agwu C, Sanna V, Jebb SA, Perna F and Fontana S. Beneficial effects of leptin on obesity T cell hypo-responsiveness and neuro-endocrine/ metabolic dysfunction of human congenital leptin deficiency. *J Clin Investig* **110**, 1093-1103, **(2002)**

64. Bray GA and Greenway FL. Current and potential drugs for treatment of obesity. *Endocr Rev* **20**, 805-875, **(1999)**

65. Haddock CK, Poston WS, Dill PL, Foreyt JP and Ericsson M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int J Obes Relat Metab Disord* **26**, 262-273, **(2002)**

66. Yanovski SZ and Yanovski JA. Obesity. *N Engl J Med* **346**, 591-602, **(2002)**

67. Kim SH, Lee YM, Jee SH and Nam CM. Effect of sibutramine on weight loss and blood pressure: a meta-analysis of controlled trials. *Obes Res* **11**, 1116-1123, **(2003)**

68. Padwal R, Majumdar SR, Johnson JA, Varney J and McAlister FA. A systematic review of drug therapy to delay or prevent type 2 diabetes. *Diabetes Care* **28**, 736-744, **(2005)**

69. Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, Hilton L, Suttorp M, Solomon V and Shekelle PG. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* **142**, 532-546, **(2005)**

70. Snow V, Barry P, Fitterman N, Qaseem A and Weiss K. Pharmacologic and surgical management of obesity in

primary care: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* **142**, 525-531, **(2005)**

71. Vettor R, Serra R, Fabris R, Pagano C and Federspil G. Effect of sibutramine on weight management and metabolic control in type 2 diabetes: a meta-analysis of clinical studies. *Diabetes Care* **28**, 942-949, **(2005)**

72. Steven E Hyman: Molecular Neuropharmacology: A Foundation for Clinical Neuroscience. McGraw-Hill Professional Illustration, **(2009)**

73. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD and Schaff HV. Valvular heart disease associated with fenfluramine-phentermine. *New Eng J Med* **337**, 581-588, **(1997)**

74. Weissman NJ. Appetite suppressants and valvular heart disease. *Amer J Med Sci* **321**, 285-291, **(2001)**

75. Meridia (sibutramine hydrochloride). American Society of Health-System Pharmacists. [http://fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm191652.htm]. **(2012)**

76. Rucker D, Padwal R, Li SK, Curioni C and Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *BMJ* **335**, 1194-1199, **(2007)**

77. Wood Shelly. Diet drug orlistat linked to kidney, pancrease injuries [theheart.org/article/1211561.do], **(2011)**

78. Bays HE. Lorcaserin: Drug profile and illustrative model of the regulatory challenges of weight-loss drug development. *Expert Rev Cardio Vasc Ther* **9**, 265-277, **(2011)**

79. Bays HE and Gadde KM. Phentermine/topiramate for weight reduction and treatment of adverse metabolic consequences in obesity. *Drugs Today* **47**, 903-914, **(2011)**

80. Maciejewski ML, Livingston EH, Smith VA, Kavee AL, Kahwati LC, Henderson WG and Arterburn DE. Survival among high-risk patients after bariatric surgery. *JAMA* **305**, 2419-2426, **(2011)**

81. Ogbonna AI, Makut MD, Gyar SD and Adamu EU. Antimicrobial activity of ethanolic extract of the seeds of Ricinus communis L. *Niger J Biotechnol* **18**, 40-43, **(2007)**

82. Ngaski MM: Phytochemical screening and proximate analysis of Cassia siamea leaves. M.Sc Thesis. Usmanu Danfodiyo University, Nigeria; **(2006)**

83. Aletor VA. Allelochemicals in plant food and feeding stuffs. I. Nutritional, biochemical and physiopathological aspects in animal production. *J Vet Hum Toxicol* **35**, 57-67, **(1993)**

84. Thompson LU. Potential health benefits and problems associated with antinutrients in foods. *Int J Food Resources* **26**, 131-149, **(1993)**

85. D'Mello JPF: Anti-nutritional factors and mycotoxins. In Farm Ani Metab Nutr. CAB International Wallingford UK; 383-403, **(2000)**

86. Morris Brad. Biofunctional legumes with nutraceutical, pharmaceutical and industrial uses. **Econ Bot 57**, 254-261, **(2003)**

87. Soetan KO and Oyewole OE. The need for adequate processing to reduce the anti-nutritional factors in animal feeds: A review. *Afr J Food Sci* **3**, 223-232, **(2009)**

88. Guil JL and Isasa MET. Nutritional composition of leaves of Chenopodium sp. *Int J Food Sci Nutr* **48**, 321-327, **(1997)**

89. Osagie AU: Antinutritional factors. In Nat Qual Plant Foods. Edited by Osagie AU and Eka OU. Nigeria; 221-244, **(1998)**

90. Oakenfull D and Sidhu GS: Saponins: Toxicants of plant origin. In CRC Press. Edited by Cheeke PR. Florida; 97-143, **(1989)**

91. Muhammad A, Dangoggo SM, Tsafe AI, Itodo AU, Atiku FA. Proximate minerals and anti-nutritional factors of Gardenia aqualla fruit pulp. *Pak J Nutr* **10**, 577-581, **(2011)**

92. Schopke TH and Hiller K. Triterpenoid saponins. *Die Pharamazie* **45**, 313-342, **(1990)**

93. Jenkins KJ and Atwal AS. Effects of dietary saponins on faecal bile acids and neutral sterols and availability of vitamins A and E in the chick. *J Nutr Biochem* **5**, 134-137, **(1994)**

94. Fenwick GR, Heaney RK and Mullin WJ. Glucosinolates and their breakdown products in foods and food plants. *Food Sci Nutr* **18**, 123-201, **(1983)**

95. You J, Wang X, Yan Y, Jin F and Huang B. Effects of active constituents of Chinese herbal medicine on HMG-CA Reductase. *Chem Abs* **120**, 70, **(1993)**

96. Waller GR, Jurzysta M and Thorne ZLR. Allelopathic activity of root saponins from alfalfa on weeds and wheat. *Bot Bull Acad Sci* **34**, 1-11, **(1993)**

97. Soetan KO, Oyekunle MA, Aiyelaagbe OO and Fafunso MA. Evaluation of the antimicrobial activity of saponins extract of Sorghumbicolor L. Moench. *Afr J Biotechnol* **5**, 2405-2407, **(2006)**

98. Okubo K, Kudou S, Uchida T, Yoshiki Y, Yoshikoshi M and Tonomura M. Soybean saponin and isoflavonoids: Structure and antiviral activity against Human Immunodeficiency virus *in vitro*. *Food Phytochem Cancer Prevent* **I**, 330-339, **(1994)**

99. Agarwal SK and Rastogi RP. Triterpenoid saponins and their genins. *Phytochemistry* **13**, 2623-2645, **(1974)**

100. Wakabayashi C, Hasegawa H, Murata T, Ichiyama M and Saiki I. Expression of *in vivo* antimetastatic effect of Ginseng protopanaxtriol saponins is mediated by their intestinal bacterial metabolites after oral administration. *J Trad Med* **14**, 180-185, **(1997)**

101. Messina MJ. Legumes and soybeans: Overview of their nutritional profiles and health effects. *Am J Clin Nutr* **70**, 439-450, **(1999)**

102. Yamaguchi A. Antidiabetics containing aqueous extract of Pittosporum plants. *Chem Abst* s129, **(1993)**

103. Marhuenda E, Marbin MJ and delaCastra CA. Anti-ulcerogenic activity of Aescine in different experimental models. *Phytother Res* **7**, 13-16, **(1993)**

104. Sagara M and Kanda TM. Effects of dietary intake of soy protein and isoflavones on cardiovascular disease risk factors in high risk, middle-aged men in Scotland. *J Am Clin Nutr* **23**, 85-91, **(2004)**

105. Just MJ, Recsio MC, Giner RM, Cuellar MJ, Marez S, Bilia AR and Rios J. Anti-inflammatory activity of usual Lupane saponins from Bulerum fruiticescens. *Planta Med* **64**, 404-407, **(1998)**

106. Huong NT, Matsumoto K, Kasai R, Yamasaki K and Watanabe H. *In vitro* anti-oxidant activity of Vietnamese Ginseng saponin and its components. *Biol Pharm Bull* **21**, 978-981, **(1998)**

107. Sofidiya MO, Odukoya OA, Familoni OB and Inya-agha SI. Free-radical scavenging activity of some Nigerian medicinal plant extracts. *Pak J Biol Sci* **9**, 1438-1441, **(2006)**

108. Ogbunugafor HA, Eneh FU,Ozumba AN, Igwo-ezikpe MN, Okpuzor J, Igwilo IO, Adenekan SO and Onyekwelu OA. Physico-chemical and anti-oxidant properties of Moringa oleifera seed oil. *Pak J Nutr* **10**, 409-414, **(2011)**

109. Ruiz-Larrea MB, Mohan AR, Raganga G, Miller NJ, Bolwell GR and Rice-Evans CA. Anti-oxidant activity of phytoestrogenic isoflavones. *Free Radic Res* **26**, 63-70, **(1997)**

110. Peterson G, Coward L, Kirk M, Falany C and Barnes S. The role of metabolism in mammary epithelial growth inhibition by the isoflavones genistein and biochanin A. *Carcinogenesis* **17**, 1861-1869, **(1996)**

111. Santibanez JF, Navarro A and Martinez J. Genistein inhibits proliferation and *in vitro* invasive potential of human prostatic cancer cell lines. *Anticancer Res* **17**, 1199-1204, **(1997)**

112. Adlercreutz H and Mazur W. Phyto-oestrogens and Western diseases. *Ann Med* **29**, 95-120, **(1997)**

113. Kim JY, Germolec DR and Luster MI. Panax ginseng as a potential immunomodulator, studies in mice. *Immunopharmacol Immunotoxicol* **12**, 257-276, **(1990)**

114. Rajkumar S, Jebanesan A. Oviposition and ovicidal activities of alkaloidal extract from Murraya koenigii against vector mosquitoes. *Nig J Nat Prod Med* **7**, 6-19, **(2003)**

115. Helsper JP, Hoogendijk JM, van Norel A and Burger-meyer K. Antinutritional factors in fababeans (Vicia faba L.) as affected by breeding toward the absence of condensed tannins. *J Agric Food Chem* **41**, 1058-1061, **(1993)**

116. Butler LG: Effects of condensed tannin on animal nutrition. Chemistry and significance of condensed tannins. Plenum Press, New York, 391-402, **(1989)**

117. Ayres MP, Clausen TP, MacLean S, Redman AM and Reichardt PB. Diversity of structure and antiherbivore activity in condensed tannins. *Ecology* **78**, 1696-1712, **(1997)**

118. Niezen JH, Waghorn TS, Charleston WAG and Waghorn GC. Growth and gastrointestinal nematode parasitism in lambs grazing either Lucerne (Medicago sativa) or sulla (Hedysarum coronarium) which contains condensed tannins. *J Agric Sci* **125**, 281-289, **(1995)**

119. Molan AL, Waghorn GC and McNabb WC. Effect of condensed tannins on egg hatching and larval development of Trichostrongylus colubriformis *in vitro*. *Vet Res* **150**, 65-69, **(2002)**

120. Lasisi OT, Soetan KO, Fafunso MA and Aiyelaagbe OO. Effects of condensed saponins on hatching of bovine gastrointestinal nematodes *in vitro*. *Niger Vet J* **24**, 30-34, **(2003)**

121. Min BR, Barry TN, Attwood GT and McNabb WC. The effect of condensed tannins on the nutrition and health of ruminants fed fresh temperate forages: a review. *Ani Feed Sci Technol* **106**, 3-19, **(2003)**

122. Igile GO: Phytochemical and Biological studies on some constituents of Vernonia amygdalina (Compositae) leaves. PhD Thesis. University of Ibadan, Department of Biochemistry; **(1995)**

123. Gatehouse AMR, Gatehouse JA, Bodie P, Kilmnoster AM and Boulter D. Biochemical basis of insect resistance in Vigna unguiculata. *J Sci Food Agric* **30**, 948-958, **(1979)**

124. Sharma HC and Norris DM. Chemical basis of resistance in soybean to cabbage looper, Trichoplusia ni. *J Sci Food Agric* **55**, 353-364, **(1991)**

125. Aletor VA: Antinutritional factors as nature's paradox in food and nutrition securities. Inaugural lecture series 15 Delivered at the Federal University of Technology, Akure on August 12, **1999**.

126. Chantre P and Lairon D. Recent findings of green tea extract AR25 (exolise) and its activity for the treatment of obesity. *Phytomedicine* **9**, 3-8, **(2002)**

127. Tziomalos K, Krassas GE and Tzotzas T. The use of sibutramine in the management of obesity and related disorders: an update. *Vasc Health Risk Manag* **5**, 441-452, **(2009)**

128. van Heerden FR. Hoodia gordonii: a natural appetite suppressant. *J Ethnopharmacol* **119**, 434-437, **(2008)**

129. Ohia SE, Opere CA, LeDay AM, Bagchi M, Bagchi D and Stohs SJ. Safety and mechanism of appetite suppression by a novel hydroxycitric acid extract (HCASX). *Mol Cell Biochem* **238**, 89-103, **(2002)**

130. Oben JE, Enyegue DM, Fomekong GI, Soukontoua YB and Agbor GA. The effect of Cissus quadrangularis (CQR-300) and a Cissus formulation (CORE) on obesity and obesity-induced oxidative stress. *Lipids Health Dis* **6**, 4, **(2007)**

131. Boschmann M and Thielecke F. The effects of epigallocatechin-3-gallate on thermogenesis and fat oxidation in obese men: a pilot study. *J Am Coll Nutr* **26**, 389-395, **(2007)**

132. Kim HK, Nelson-Dooley C, Della-Fera MA, Yang JY, Zhang W, Duan J, Hartzell DL, Hamrick MW and Baile CA. Genistein decreases food intake, body weight, and fat pad weight and causes adipose tissue apoptosis in ovariectomized female mice. *J Nutr* **136**, 409-414, **(2006)**

133. Attele AS, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, Pugh W, Rue PA, Polonsky KS and Yuan CS. Antidiabetic effects of Panax ginseng berry extract and the identification of an effective component. *Diabetes* **51**, 1851-1858, **(2002)**

134. Yang JY, Della-Fera MA and Baile CA. Guggulsterone inhibits adipocyte differentiation and induces apoptosis in 3T3-L1 cells. *Obesity (Silver Spring)* **16**, 16-22, **(2008)**

135. Puri M, Sharma D and Barrow CJ. Enzyme-assisted extraction of bioactives from plants. *Trends in Biotechnol* **30**, 37-44, **(2012)**

136. Armand M. Lipases and lipolysis in the human digestive tract: where do we stand? *Curr Opin Clin Nutr Metab Care* **10**, 156-164, **(2007)**

137. Raghavendra MP and Prakash V. Phenylboronic acid-a potent inhibitor of lipase from Oryza sativa. *J Agric Food Chem* **50**, 6037-6041, **(2002)**

138. Ninomiya K, Matsuda H, Shimoda H, Nishida N, Kasajima N, Yoshino T, Morikawa T and Yoshikawa M. Carnosic acid, a new class of lipid absorption inhibitor from sage. *Bioorg Med Chem Lett* **14**, 1943-1946, **(2004)**

139. Han LK, Zheng YN, Xu BJ, Okuda H and Kimura Y. Saponins from Platycodi radix ameliorate high fat diet induced obesity in mice. *J Nutr* **132**, 2241-2245, **(2002)**

140. Zhao HL and Kim YS. Determination of the kinetic properties of platycodin D for the inhibition of pancreatic lipase using a 1,2-diglyceride-based colorimetric assay. *Arch Pharm Res* **27**, 968-972, **(2004)**

141. Zhao HL, Sim J, Shim SH, Ha YW, Kang SS and Kim YS. Antiobese and hypolipidemic effects of Platycodin saponins in diet-induced obese rats: evidences for lipase inhibition and calorie intake restriction. *Int J Obes* **29**, 983-990, **(2005)**

142. Won S, Kim S, Kim Y, Lee P, Ryu J and Kim J. Licochalcone A: a lipase inhibitor from the roots of Glycyrrhiza uralensis. *Food Res Intern* **40**, 1046-1050, **(2007)**

143. Zheng Q and Koike K. New biologically active triterpenoid saponins from Scabiosa tschiliensis. *J Nat Prod* **67**, 604-613, **(2004)**

144. Yoshizumi K, Hirano K, Ando H, Hirai Y, Ida Y, Tsuji T, Tanaka T, Satouchi K and Terao J. Lupane type saponins from leaves of Acanthopanax sessiliflorus and their inhibitory activity on pancreatic lipase. *J Agric Food Chem* **54**, 335-341, **(2006)**

145. Han LK, Zheng YN, Yoshikawa M, Okuda H and Kimura Y. Anti-obesity effects of chikusetsu saponins isolated from Panax japonicus rhizomes. *BMC Complement Altern Med* **5**, 9-18, **(2005)**

146. Kwon C, Sohn H, Kim S, Kim J, Son K and Lee J. Anti-obesity effect of Dioscorea nipponica Makino with lipase-inhibitory activity in rodents. *Biosci Biotechnol Biochem* **67**, 1451-1456, **(2003)**

147. Kimura H, Ogawa S, Jisaka M, Kimura Y, Katsube T and Yokota K. Identification of novel saponins from edible seeds of Japanese horse chestnut (Aesculus turbinata Blume) after treatment with wooden ashes and their nutraceutical activity. *J Pharm Biomed Anal* **41**, 1657-1665, **(2006)**

148. Kurihara H, Asami S, Shibata H, Fukami H and Tanaka T. Hypolipemic effect of Cyclocarya paliurus (Batal) Iljinskaja in lipid-loaded mice. *Biol Pharm Bull* **26**, 383-385, **(2003)**

149. Sheng L, Qian Z, Zheng S and Xi L. Mechanism of hypolipidemic effect of crocin in rats: Crocin inhibits pancreatic lipase. *Eur J Pharmacol* **543**, 116-122, **(2006)**

150. Lowe M. The triglyceride lipases of the pancreas. *J Lipid Res* **43**, 2007-2016, **(2002)**

151. Kopelman P, Bryson A, Hickling R, Rissanen A, Rossner S and Toubro S. Cetilistat (ATL-962), a novel lipase inhibitor: a 12-week randomized, placebo-controlled study

of weight reduction in obese patients. *Int J Obes* **31**, 494-499, **(2007)**

152. Filippatos T, Derdemezis C, Gazi I, Nakou E, Mikhailidis D and Elisaf M. Orlistat-associated adverse effects and drug interactions: a critical review. *Drug Saf* **31**, 53-65, **(2008)**

153. Moreno D, Ilic N, Poulev A and Raskin I. Effects of Arachis hypogaea nutshell extract on lipid metabolic enzymes and obesity parameters. *Life Sci* **78**, 2797-2803, **(2006a)**

154. Moreno DA, Ripoll C, Ilic N, Poulev A, Aubin C and Raskin I. Inhibition of lipid metabolic enzymes using Mangifera indica extracts. *J Food Agric Environ* **4**, 21-26, **(2006b)**

155. Kobayashi K, Ihara S, Kobata A, Itoh K, Kusunoki N and Yoshizaki F. Inhibitory effect of Myrica bark on lipase activity in mouse plasma and gastrointestinal tract. *J Med Food* **11**, 289-293, **(2008a)**

156. Kobayashi K, Yamada K, Murata T, Hasegawa T, Takano F and Koga K. Constituents of Rhodiola rosea showing inhibitory effect on lipase activity in mouse plasma and alimentary canal. *Planta Med* **74**, 1716-1719, **(2008b)**

157. Gholamhoseinian A, Shahouzehi B and Sharifi-far F. Inhibitory effects of some plant extracts on pancreatic lipase. *Int J Pharm* **6**, 18-24, **(2010)**

158. Harach T, Aprikian O, Monnard I, Moulin J, Membrez M and Bolor J. Rosemary (Rosmarinus officinalis L.) leaf extract limits weight gain and liver steatosis in mice fed a high-fat diet. *Planta Med* **76**, 566-571, **(2010)**

159. Roh C and Jung U. Screening of crude plant extracts with anti-obesity activity. *Int J Mol Sci* **13**, 1710-1719, **(2012)**

160. Mizutani T, Inatomi S, Inazu A and Kawahara E. Hypolipidemic effect of Pleurotus eryngii extract in fat-loaded mice. *J Nutr Sci Vitaminol* **56**, 48-53, **(2010)**

161. Lee JK, Song JH and Lee JS. Optimal extraction conditions of anti-obesity lipase inhibitor from Phellinus linteus and nutritional characteristics of the extracts. *Mycobiology* **38**, 58-61, **(2010)**

162. Tsujita TH, Takaichi T, Takaku T, Sawai N, Yoshida and Hiraki J. Inhibition of lipase activities by basic polysaccharide. *J Lipid Res* **48**, 358-365, **(2007)**

163. Tsujita T,Sumiyoshi M, TakakuT, MomsenWE, Lowe ME and Brockman HL. Inhibition of lipases by ε-polylysine. *J Lipid Res* **44**, 2278-2286, **(2003)**

164. Tsujita T, Matsuura Y and Okuda H. Studies on the inhibition of pancreatic and carboxylester lipases by protamine. *J Lipid Res* **37**, 1481-1487, **(1996)**

165. Lairon D. Effects of dietary fibers and cholestyramine on the activity of pancreatic lipase *in vitro*. *Amer J Clin Nutr* **42**, 629-638, **(1985)**

166. Garpun Y, Julien R, Pieroni G, Verger R and Sarda L. Studies on the inhibition of pancreatic and microbial lipases by soybean proteins. *J Lipid Res* **25**, 1214-1221, **(1984)**

167. Bose M, Lambert J, Ju J, Reuhl K, Shapses S and Yang C. The major green tea polyphenol, (-)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome and fatty liver disease in high-fat-fed mice. *J Nutr* **138**, 1677-1683, **(2008)**

168. Yamamoto M, Shimura S, Itoh Y, Ohsaka T, Egawa M and Inoue S. Anti-obesity effects of lipase inhibitor CT-II, an extract from edible herbs, Nomame Herba, on rats fed a high-fat diet. *Int J Obes Relat Metab Disord* **24**, 758-764, **(2000)**

169. Sugiyama H, Akazome Y,Shoji T, Yamaguchi A,Yasue M, Kanda T and Ohtake Y. Oligomeric procyanidins in apple polyphenol are main active components for inhibition of pancreatic lipase and triglyceride absorption. *J Agric Food Chem* **55**, 4604-4609, **(2007)**

170. Shimoda H, Seki E and Aitani M. Inhibitory effect of green coffee bean extract on fat accumulation and body weight gain in mice. *BMC Complement Altern Med* **6**, 9, **(2006)**

171. Jager S, Trojan H, Kopp T, Laszczyk M and Scheffler A. Pentacyclic triterpene distribution in various plants - rich sources for a new group of multi-potent plant extracts. *Molecules* **14**, 2016-2031, **(2009)**

172. Cha Y, Rhee S and Heo Y. Acanthopanax senticosus extract prepared from cultured cells decreases adiposity and obesity indices in C57BL/6J mice fed a high fat diet. *J Med Food* **7**, 422-429, **(2004)**

173. Li F, Li W, Fu H, Zhang Q and Koike K. Pancreatic lipase-inhibiting triterpenoid saponins from fruits of Acanthopanax senticosus. Chem Pharm Bull 55: 1087-1089. **(2007)**

174. Yoshizumi K, Murota K, Watanabe S, Tomi H, Tsuji T and Terao J. Chiisanoside is not absorbed but inhibits oil absorption in the small intestine of rodents. *Biosci Biotechnol Biochem* **72**, 1126-1129, **(2008)**

175. Kimura H, Ogawa S, Katsube T, Jisaka M and Yokota K. Antiobese effects of novel saponins from edible seeds of Japanese horse chestnut (Aesculus turbinatablume) after treatment with wood ashes. *J Agric Food Chem* **56**, 4783-4788, **(2008)**

176. Han L, Nose R, Li W, Gong X, Zheng Y and Yoshikawa M. Reduction of fat storage in mice fed a high-fat diet long term by treatment with saponins prepared from Kochia scoparia fruit. *Phytother Res* **20**, 877-882, **(2006)**

177. Karu N, Reifen R and Kerem Z. Weight gain reduction in mice fed Panax ginseng saponin, a pancreatic lipase inhibitor. *J Agric Food Chem* **55**, 2824-2828, **(2007)**

178. Martins F, Noso T, Porto V, Curiel A, Gambero A and Bastos DHM. Mate tea inhibits *in vitro* pancreatic lipase activity and has hypolipidemic effect on high-fat diet-induced obese mice. *Obesity* **18**, 42-47, **(2010)**

179. Han LK, Kimura Y, Kawashima M, Takaku T, Taniyama T, Hayashi T, Zheng YN and Okuda H. Anti-obesity action of oolong tea. *Int J Obes* **23**, 98-105, **(1999)**

180. Nakai M, Fukui Y, Asami S, Toyoda-Ono Y, Iwashita T, Shibata H, Mitsunaga T, Hashimoto F and Kiso Y. Inhibitory effects of oolong tea polyphenols on pancreatic lipase *in vitro*. *J Agric Food Chem* **53**, 4593-4598, **(2005)**

181. Ono Y, Hattori E, Fukaya Y, Imai S and Ohizumi Y. Anti-obesity effect of Nelumbo nucifera leaves extract in mice and rats. *J Ethnopharmacol* **106**, 238-244, **(2006)**

182. Yoshikawa M, Shimoda H, Nishida N, Takada M and Matsuda H. Salacia reticulata and its polyphenolic constituents with lipase inhibitory and lipolytic activities have mild antiobesity effects in rats. *J Nutr* **132**, 1819-1824, **(2002)**

183. Mutoh M, Nakada N, Matsukuma S, Ohshima S, Yoshinari K and Watanabe J. Panclicins, novel pancreatic lipase inhibitors.Taxonomy, fermentation, isolation and biological activity. *J Antibiot* **47**, 1369-1375, **(1994)**

184. Yoshinari K, Aoki M, Ohtsuka T, Nakayama N, Itezono Y, Mutoh M, Watanabe J and Yokose K. Panclicins, novel pancreatic lipase inhibitors II. Structural elucidation. *J Antibiot* **47**, 1376-1384, **(1994)**

185. Nonaka Y, Ohtaki H, Ohtsuka E, Kocha T, Fukuda T and Takeuchi T. Effects of ebelactone B, a lipase inhibitor, on intestinal fat absorption in the rat. *J Enzym Inhib* **10**, 57-63, **(1996)**

186. Liu DZ, Wang F, Liao TG, Tang JG, Steglich W, Zhu HJ and Liu JK. Vibralactone: a lipase inhibitor with an unusual fused lactone produced by cultures of the basidiomycete Boreostereum vibrans. *Org Lett* **8**, 5749-5752, **(2006)**

187. Kim J, Kim H, Park H, Youn S, Choi D and Shin C. Development of inhibitors against lipase and alpha-glucosidase from derivatives of monascus pigment. *FEMS Microbiol Lett* **276**, 93-98, **(2007)**

188. Tomoda H, Namatame I and Omura S. Microbial metabolites with inhibitory activity against lipid metabolism. *Proc Japan Acad* **78**, 217-240, **(2002)**

189. Kitahara M, Asano M, Naganawa H, Maeda K, Hamada M, Aoyagi T, Umezawa H, Iitaka Y and Nakamura H. Valilactone, an inhibitor of esterase, produced by actinomycetes. *J Antibiot* **40**, 1647-1650, **(1987)**

190. Umezawa H, Aoyagi T, Hazato T, Uotani K, Kojima F, Hamada M and Takeuchi T. Esterastin, an inhibitor of esterase produced by actinomycetes. *J Antibiot* **31**, 639-641, **(1978)**

191. Cordula. Percyquinnin, a process for its production and its use as a pharmaceutical [http://patentscope.wipo.int/search/en/WO2001077094], **(2001)**

192. Matsumoto M, Hosokawa M, Matsukawa N, Hagio M, Shinoki A, Nishimukai M, Miyashita K, Yajima T and Hara H. Suppressive effects of the marine carotenoids, fucoxanthin and fucoxanthinol on triglyceride absorption in lymph duct-cannulated rats. *Eur J Nutr* **49**, 243-249, **(2010)**