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Pharmacological treatments and natural for obesity: literature review and patents

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Abstract: Obesity is a multifactorial disease that causes development and / or progression of several other diseases. Although there are several ways to treat obesity like diet, physical activity, re-education, and surgery, search for medications as adjuncts to treatment continues to increase. Scientific community has been researching new drugs and natural compounds that aim to increase efficiency of antiobesity treatment and reduce side effects associated with the use of medication. In order to contribute to updating of this relevant subject, this review compiled most recent studies included in the *Science Direct* journal platform on different approaches to contain disease progression, including drugs used in treatment of other diseases and have been shown to be efficient as antiobesity agentes, natural plant compounds having pancreatic lipase inhibition activity. In addition to more recent experiments on subject, this article has made search for patent deposits using European Espacenet database to check how many of most recent experiments have turned into drugs.

Keywords: Obesity, pancreatic lipase inhibitor, chemical treatments, fruits, articles, patents.

I. Introduction

Obesity has been recognized worldwide as multifactorial disorder caused by interaction of genetic, lifestyle, environmental and nutritional factors [1]. This disease causes inflammatory process in body leading to development and / or progression of several other non-contagious diseases. With estimated 2.8 million deaths year, obesity contributes to increased risk of global deaths [2].

Before 18th century obesity was treated compassionately as sign of financial status (if you were fat because you had lots of money and you ate well). Word obesity was not part of popular parlance, term "corpulent subject" was more commonly used to refer to an obese man. According to historian Georges Vigarello [3] in book "The Metamorphoses of Fat - History of Obesity" only in 18th century came measurements of degrees of fat and idea that fatter ones represent not only a quantitative excess but a disorder. From 19th century, obesity came to be seen with an evil that needed to be fought at all costs and obese labeled as lazy, sick, slow, ugly and incapable. And this has led to consumption of drugs to combat weight gain, often not associated with a healthier lifestyle and constant practice of physical exercises.

Williams et al.[4] defines obesity as a multifactorial disease, characterized by overweight for height due to an extended fat deposition as adipose tissue, which is attributed to a higher calorie intake than energy expenditure. At cellular level is characterized by an increase in number and size of adipocytes (fat storage cells) in tissue. Irrespective of relationship between adiposity and inflammation being established, there is gradually recognition that adipose also produce inflammatory cytokines, suggesting that obesity induces an inflammatory state, which can lead to disease progression.

This increase in obese people in world has multi-factor causes then the treatment should also be multifactorial and usually involve mechanisms to decrease ingestion, absorption of carbohydrates, lipids, increase in physical activity, decrease lipogenesis and increase lipolysis, control of hormones that regulate hunger and satiety. One is dysfunction of ghrelin hormones that stimulate appetite, leptin produced by adipose cells that acts on central nervous system indicating satiety. This malfunction can be caused by diseases or unbalanced intake of nutrients causing body to not respond more effectively to these commands of central nervous system causing person to consume many foods without feeling satiated. Objective of this study was to analyze pharmacological, natural advances used in treatment of obesity, mainly pancreatic lipase inhibitors.

II. Growing interest in obesity by universities and research centers

In last three decades, with an alarming increase in number of obese [5], public expenditures with this disease, its associated effects (respiratory, digestive and circulatory) that became a morbid and metabolic occurrence that needed to be treated. A base of journals *Science direct* [6] is one of most updated in world maintaining in single environment diverse articles from different periodicals. **Table 1** shows research of

scientific articles condu cted in April 2019 using *Science Direct* platform, which includes access to approximately 2.500 scientific journals and more than 26.000 e-books in a single virtual environment.

It can be noted by Table 1 when doing a search in *Science Direct* using descriptor "obesity" can get 430, 870 articles, 75,855 articles were published between years 2017-2019. Other descriptors used (Anti-obesity, Drugs obesity, Lipase inhibitor, Polyphenols and obesity, Fruit extracts and obesity) have also been subjects very much approached in recent research in different countries. This great concern with this theme its developments in universities, academies, study centers has been proven with increase in number of articles published in several journals aiming to discover new treatments and / or coadjuvantes for weight reduction [7].

III. Scientific evidence of deleterious effects of obesity

This excess in food consumption is considered global epidemic [8], regardless of economic, social conditions, manifests itself as abnormal, excessive increase or accumulation of energy in form of fat in adipose tissue [9]. Researchers report that in 95% of cases of obesity, main cause is nutritional, exogenous or primary, while it is endogenous, monoergic or secondary, cause in 5% [5]. By 2016, over 650 million adults were considered obese, representing approximately 13% of world's adult population. At present, it is estimated that more than 340 million children and adolescents aged 5 to 19 years are overweight or obese, a prevalence of 18% in this age group [10], [8].

Big problem of current century is to make people aware that avoiding obesity is not a question of aesthetics but rather of public health, providing people with healthier alternatives than synthetic drugs to improve quality of life. Phenolics of natural products supply this need when used in association with other healthy practices. Although it is not appropriate to undermine intellectual ability or be prejudiced against obese people, scientific evidence corroborates that obesity is important risk factor for cardiovascular disease, type 2 diabetes mellitus, dyslipidemia, insulin resistance and metabolic syndrome [11], [12], adipocytes released from adipose tissue have profound effects on fertility in males, gallbladder disease, orthopedic problems, adipocytes released from adipose tissue have profound effects on fertility in men, hepatic steatosis [13], [14].

Epidemiological studies support a possible link between obesity and risk of breast, colon, pancreatic and cervical cancer, as well melanoma, with approximately 20% of all diagnosed cancers being attributed to obesity, overweight. Precise mechanisms of tumor progression related to obesity are still unclear; studies aimed at accurately deciphering progression of cancer are scarce. In order to neutralize tumor containing effect of obesity, adipokines [15] there is increasing interest in exploring possibility of weight loss therapies, natural or chemical treatments that can reduce cancer-related deaths.

IV. Inhibition of pancreatic lipase: natural products and Pharmacological

In addition, pancreatic lipase is main enzyme for transport and uptake of cholesterol from lipid emulsion to intestinal cells, is responsible for hydrolysis of 50-70% of total dietary fat [16]. All problems associated with obesity serve as justification for intensifying studies on this syndrome, less aggressive treatments to treat it.

In addition to its importance digestion, transport, processing of lipids diet, lipases act in hydrolysis of variety of lipid substrates to modulate membrane integrity, lipid signaling, production, dynamics of lipid rafts. Lipase substrates are diverse, including neutral lipids, phospholipids, lysophospholipids, sphing lipids, ether lipids, oxidized lipids, lipid fractions post-translationally added to proteins [17].

Inhibition pancreatic lipase is mechanism of interest for study, development various drugs for treatment of obesity induced by diet because their effects are more tolerated by human body. Pancreatic lipase is primary digestive enzyme secreted by pancreatic exocrine [2], that removes fatty acids from triglycerides, which produce lipolytic product, monoglyceride and polyunsaturated long chain fatty acids. In addition, inhibition of pancreatic lipase is one of most widely studied mechanisms to determine antiobesity activity of several products [16]. Between years of 2016-2019 have already been placed in *Science Direct* [6] 3,028 articles on this subject. Of these 850 articles were identified as review articles and 1,166 were original articles. **Table 2** lists some original articles aimed at testing, proving efficiency of pancreatic lipase inhibitors from variety of sources, especially natural products.

Pharmacological inhibition of certain lipases has caused number of therapeutic benefits. Because of this, some lipases have been targeted by pharmaceutical companies for therapeutic benefit, there are several drugs that are currently approved or clinical trials for treatment of obesity, pain, inflammation, anxiety, cardiovascular diseases [31], [32]. However, inhibition of some lipases by environmental chemicals has also been shown cause pathologies ranging from neurodegeneration to psychotropic effects to dyslipidemia [33]. Even with side effects most commonly used drugs are Orlistat (pancreatic lipase inhibitor), Lorcaserim (controlling the appetite through receptors in the brain).

IV.1 Pharmacological treatments: Orlistat, Lorcaserin and new antiobesity therapies

Pharmacological treatments approved by Food and Drug Administration (FDA) have been kept constant, this may have motivated increase of research and patent deposits of various drugs used in treatment of obesity or that were used for another purpose but were also effective in weight loss. Anti-obesity drugs can produce weight loss with considerable variation in treatment response. Food and Drug Administration (FDA) and European Medicines Agency (EMA) are responsible for ensuring safety and efficacy of pharmacotherapy before providing marketing approval for a drug.

Regarding pharmacological treatment of obesity, only four drugs were registered between 1996 and 2011: Dexfenfluramine (Redux®), Sibutramine (Meridia®, Reductil®), Orlistat (Xenical®) and Rimonabant (Acomplia®). More recently, Lorcaserin (Belviq®) and a sustained release formulation of Phentermine and Topiramato (Qsymia TM) have been approved by FDA (June and July 2012, respectively). Of these drugs, Sibutramine, Phentermine, Dexfenfluramine and Rimonabant have already been marketed because of serious side effects associated with its use, and Orlistat and Lorcaserin [33] have been released for prolonged use.

Obesity has been commonly treated with Roche's Orlistat, commercially known as Xenical, Redustat, Slimella, Beltas, Redicres or Alli. It is a hydrogenated derivative of *Streptomyces toxitricini* lipstatin, approved by Food and Drug Administration (FDA) in 1999 and has been found to be effective, relatively tolerable and safe in treatment of human obesity [34].

Orlistat works primarily by preventing absorption of dietary lipids through reversible inhibition of gastrointestinal lipases [15] and can reduce dietary fat absorption by up to 30%, being most commonly used weight-reducing agent [35]. Absorption of Orlistat and metabolism are minimal, 83% of drug is mainly eliminated intact in faeces. Studies have shown that in patients treated with Orlistat there was a significant reduction of low-density lipoprotein (LDL), triglyceride levels (TGs), plasma cholesterol and weight loss [36].

However, prolonged consumption of this drug has caused unpleasant side effects such as diarrhea, nausea, gastric irritation, skin blemishes, flatulence, fecal incontinence and dry skin [34]. Some researchers have related the excessive use of Orlistat with the increase of cases of bulimia nervosa in young people [37]. Studies suggest that therapy with Orlistat may induce formation of oxalate of nephropathy [38] although other factors may contribute to development of renal diseases.

According to FDA [39] between April 1999 and August 2009 about 40 million people worldwide who used Xenical or Alli. Some patients (a case in the USA with Alli and 12 foreign cases with Xenical) have reported development of severe liver damage, although they claim that they also used other drugs or had other conditions that may have contributed to development of disease. Of these patients, two died of liver failure and three patients required liver transplantation. These cases associated with data from clinical trials or preclinical studies prompted the FDA to include information on severe liver damage on label of Xenical and Alli. This alert is important though, a serious liver injury can occur in people who do not take drugs and without a different cause.

In 2012, *Lorcaserim hydrochloride* marketed as Belviq or Qsymia, manufactured by Arena Pharmaceuticals, was first weight loss pill approved by American government in 13 years. FDA has approved marketing of this drug for obese adults and with at least one of diseases related to being overweight, such as hypertension or diabetes. Drug works by controlling appetite through receptors in brain through activation of serotonin 2C receptor. Clinical trials showed that drug helped patients lose an average of 3 to 3.7% of their body weight after a year compared to a placebo. Drug has been approved for use in obese adults with a body mass index (BMI) of 30 or more and in overweight adults with a BMI of 27 or higher who have at least one disease related to overweight such as hypertension, dyslipidemia, type 2 diabetes or high cholesterol [33].

Table 3 depicts experiments with several recently used drugs and some have proven their effectiveness in containing advances of obesity. Some of new drugs were already used to treat other diseases such as depression, diabetes, anorexia, bulimia are effective in reducing weight and reducing appetite.

Most common side effects of Lorcaserin are: headache, dizziness, fatigue, nausea, dry mouth and constipation in non-diabetic individuals; hypoglycemia, back pain, coughing and fatigue in diabetic individuals. Lorcaserim should be used with caution in patients with congestive heart failure, because the number of 5-HT2B receptors is possibly increased in this pathology [20]. Although these drugs are already consolidated in world market, pharmaceutical industry continues to invest in research on new drugs or reduce effects of obesity or treat other diseases such as diabetes or depression and which has an auxiliary effect on weight loss

Phentermine is central norepinephrine release drug, approved for treatment of short-term obesity at 15-037.6 mg / day, remains most prescribed anti-obesity drug in US. *Topiramate* is drug that has several mechanisms of action, is marketed for treatment of epilepsy, migraine prophylaxis. It was evaluated alone for weight reduction in obese patients without, with type 2 diabetes, hypertension. Topiramate, phentermine are

widely prescribed drugs are considered safe, tolerable. Treatment with phentermine and topiramate was generally well with some side effects well tolerated by users such as: dry mouth, constipation, paresthesia being most common adverse events. Combination of phentermine and topiramate was effective in both doses in reducing weight and improving cardiometabolic variables in population of patients - obese individuals with two or more comorbidities [50].

Over past three decades, *Melanocortin antagonists* have received attention as potential analgesics for treatment of chronic pain and melanocortin peptides regulate pain through two classes of melanocortinergic receptors known as melanocortin-1 (MC1R) and melanocortin-4 (MC4R). MC4R is important regulator of glucose balance, food intake, energy homeostasis to maintain body weight, evidence suggest that MC4Rs are widely expressed in central nervous system [42], [30].

Glucagon-like peptide (GLP) -1 is incretin hormone that has been shown to affect glucose, lipid, hepatic metabolism. Liraglutide, a GLP-1 analogue with 97% identity to human GLP-1, is currently being used new therapy for glucose control [14], reduces oxidative stress, inflammatory response in liver in experiments with mice [31]. All these effects are mediated by activation of GLP-1 [14].

Glucocorticoids are routinely employed for control, treatment of diseases, inflammatory, autoimmune [43], but their pleiotropic nature leads to harmful metabolic side effects [43]. Quarta et al. [51 developed specific tissue anti-inflammatory agent in which GLP-1 selectively delivers dexamethasone to cells expressing GLP-1 receptor, ignoring many of deleterious side effects of chronic dexamethasone treatment. GLP-1 / Dexa anti-inflammatory agent improves metabolism, reduces body weight in up to 25% obese rats through central, peripheral effects.

Linifanib is potent selective inhibitor of vascular endothelial growth factor, platelet-derived growth factor tyrosine kinase activity, has clinical activity advanced non-small lung cancer (NSCLC) in both monotherapy outbreak, carboplatin and paclitaxelin [52]. Liniab agent is effectiv treating cancer. A wide spectrum of tumor types is inhibited by Linifanib, including small cell lung cancer, carcinoma of colon (CRC), carcinoma (BC), and gastric cancer. Recently it has been discovered that this agent has promising anti-obesity effect promoting dimming of adipocytes, inhibiting adipogenesis [42], [53].

Naltrexone is opioid antagonist with high affinity for FDA-approved opioid receptor initially for treatment of alcoholism, opiate dependence, it has been noted that substance influences food intake, body weight. Studies humans demonstrate that opioids can influence bowel behavior by modulating subjective palatability. Opioids act on rewarding aspects of eating, naltrexone reduces subjective pleasure, or taste, certain foods (especially tasty foods); this effect is independent of nausea, common side effect of naltrexone. *Bupropion* is atypical antidepressant currently approved for treatment of depression and seasonal affective disorder. Bupropion reduces short-term food intake in lean, obese models, increases energy expenditure by increasing heat production . Injection of *bupropion* alone or naltrexone alone directly into reward system is sufficient to reduce food intake in hungry mice. However, direct injection of naltrexone and bupropion produces synergistic (greater than additive) reduction in food consumption, indicating that naltrexone, bupropionate have independent and complementary actions in rewards system [54].

Metformin (dimethylbiguanide) is antihyperglycemic, insulin sensitizing agent used in treatment of non-insulin dependent type 2 diabetes mellitus. Accumulated evidence indicates that metformin pharmacodynamics is not only determined by activated protein kinase activation, which decreases blood glucose production but is also influenced by intestinal microbiota [55], [32]. In their studies Kim et al. [49] showed the effectiveness of Metformin in reducing body weight. Pharmaceutical industry continues to show interest in new drugs or new drug functions already used in treatment of other diseases, although some authors suggest that most recommended is not single approach such as pharmacological treatment but multidisciplinary intervention including behavioral therapy, diet use of transcranial stimulation in treatment of hypertension, well use of transcranial stimulation by direct current [46], [2], [1], [40], acupuncture with herbs [41].

Although use of drugs has its importance to contain effects of obesity it is noted that often, people have exceeded use, further increasing its side effects. In addition, benefits are discontinued, such as weight loss after cessation of drug use. These problems have motivated several studies aiming at finding efficient, less aggressive natural substitutes to treat obesity, its health problems.

IV.2 Polyphenols as antiobesity agents

Use of medicinal plants in treatment, prevention of diseases is old as human species. Studies with several plants have been promising in scientific environment and provided discovery of pharmacological properties of several plants, fruits, their pomaces. **Table 4** lists studies with antiobesity effects using various plants, fruits, phenolic compounds or natural plant constituents. It is important to note that these plants have

chemical components similar to tannins, terpenoids, flavonoids, pectin polysaccharides, anthocyanins, fibers, prebiotcs, already mentioned in literature as efficient in treatment of obesity due to its efficiency as thermogenics, weight reduction, increase in satiety, decrease of LDL cholesterol, inhibitors of pancreatic lipase and antioxidants.

In most studies looking for compounds for treatment of obesity there is tendency for researchers to remove polyphenols from leaves, stems and roots. More recently some researchers have noted that fruit pomace remains high in insoluble fiber, variety of bioactive compounds, antioxidant activity and potential to inhibit pancreatic lipase (**Table 5**).

Polyphenols are widely distributed among plant parts have been constantly studied because of their antioxidant capacity, directly influencing activities of key enzymes. Rahim et al. [85] also analyzed kinetics of inhibition of flavonoid non-flavonoid polyphenols on pancreatic lipase. Few fruits have been tested for this purpose, although they have phenolic compounds associated to reduction of lipids and often quantities superior to those found other parts of plants. Homoki et al. [17] analyzing functional mechanisms of anthocyanins found that they have α-amylase inhibition, anti-diabetes and anti-obesity properties. Inhibitors of lipase similar to epigallocatechin-3-gallate, grape seed, canferol, quercetin, ellagitanine, tannins and proanthocyanidins are present in green and black tea, blackberry, grape, strawberry and blueberry [86].

Recent animal studies point to potential of using resveratrol in prevention and / or treatment of obesity: demonstrating protective effect of resveratrol on obesity induced by hyperlipid diet (HFD) and changes in oxidative stress in rabbits [87]. Yingjie et al. [88] have demonstrated that resveratrol attenuates hyperlipidemia-induced cardiomyopathy by regulating estrogen-associated α-α receptor. Gu, Yu & Lambert [89] reported that use of powdered cocoa supplementation reduced weight gain, inflammation of obesity, insulin resistance, hepatic steatosis, pro-inflammatory gene expression in white adipose tissues (WAT) of rats hyperlipid diet. Antioxidants cocoa polyphenols can modify glycemic index response, lipid profile, decrease platelet aggregation, inflammation and blood pressure.

V. Depósito de Patentes

Although polyphenol research is very promising for treatment of obesity, it should be emphasized that no single drug or nutraceutical used alone will have a lasting and satisfactory effect. What it seems is that people have far exceeded use of drugs and now far exceed use of natural products often taking several together. It is necessary to invest much more in disease prevention, population awareness of dangers associated with obesity and that weight control is not question of aesthetics or personal preference but rather health.

In consultation with European patent base Espacenet [90], first search was made in 2017 (1975 to 2016), through its online search system, with national patents of National Institute of Industrial Property of Brazil (INPI), international patents (European Patent Office (EPO), World Intellectual Property Organization (WIPO), United States Patent and Trademark Office (USPTO) encompassing about 90 countries using descriptors related to "obesity treatments" to assess how many studies to some drug or nutraceutical (**Table 6**).

This indicates that research into finding new drugs has been frequent and meets the call of most people to find remedy that will promptly resolve their weight gain problems without the need for too much effort. Although people consciously understand that treating obesity, its effects involves lot of discipline, many factors (controlling eating, exercise, healthy eating, etc.), tendency of most has been to seek "magic formulas", diversity of drugs seems to wish. Among these researches at Espacenet [90], some countries have distinguished themselves in development of drugs for treatment of obesity: United States (33 patents), South Korea (32 patents), China (16 patents), Japan (13 patents), Taiwan (6 patents), European Patent Organization (5 patents) and Canada and South Africa (4 patents each). Countries such as Italy, Mexico, Ireland, Hong Kong, Russian Federation, Yugoslavia / Serbia and Montenegro, Greece, New Zealand, India have only one patent each. For the survey of articles were used the bases Scielo, and Science Direct.

Consultation with Espacenet in 2019 revealed an increase in number of research on new drugs to treat obesity. Total number of patents increased from 26,719 (2016) to 30,274 (2019). In all descriptors there were increases in number of patents deposited. It is important to note that in 3 year period there were 59 new compounds with potential to inhibit pancreatic lipase, 51 new patents associated with fruit extracts and obesity treatment. These data prove that researchers have recognized the effectiveness of fruit compounds in treating disease, has focused their studies on that aspect. We can infer from this data that most of discovered lipase inhibitors come from natural sources, that there is still a very broad field for discovery, development of new drugs to serve as coadjuvant in treatment of obesity.

VI. Conclusion

1. As obesity is a multifactorial disease its treatment should also involve various aspects and approaches.

2. Obesity involves several risks as it induces the body to the inflammatory state, so it should be treated as a disease and not as a simple matter of aesthetic beauty.

3. Several drugs have been used to reduce weight and contain the effects of obesity each with a different mode of action.

4. Some drugs used to contain other diseases such as depression and anxiety have been shown to be effective in treating obesity.

5. Many university-developed studies on obesity inhibitors and appetite suppressants have been patented and marketed today.

6. Pancreatic lipase inhibitors from natural sources have been the target of much research because they are efficient and have fewer side effects than chemical inhibitors.

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Conflicts of interest

Author declare that they do not have a conflito finterestin any capacityi ncluding competingor financial.

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Table 1: Researches of scientific articles in Science Direct platform using different descriptors that are in title of journal.

Descriptors	**Bases of periodicals**	
	Science Direct (2014-2016)	*Science Direct* (2017-2019)
Obesity	430, 870	75,855
Anti-obesity	141,596	177,47
Drugs obesity	162,434	28,652
Lipase inhibitor	58,654	7,649
Polyphenols and obesity	8,233	2,974
Fruit extracts and obesity	7,636	2,383
Total	809,423	294,983

Table 2: Compounds and plants recently reported in studies on pancreatic lipase inhibition.

Compound and / or plant	**Usedpart and/or compound**	**References**
Trigonella foenum-graecum	Seed	Fernando et al., 2019 [16]
Indol glioxilamidas	Chemical aromatic compound	Sridhar et al., 2019[2]
Quinoa and fenugreek	Seed extracts	Herrera et al., 2019 [18][
Benzimidazole	Derivatives compound	Mentense et al., 2019 [19]
Cornus alba *Cornus mas*	Hydroxytyrosol glucoside Loganic acid and cornuside	Świerczewskaet al., 2019 [20]
Cassia grandis Lf	Pulp fruit (nanodisperion)	Prada et al., 2019 [21]
Ginkgo biloba *Cortex Mori* Radicis	Biflavones Herva chinesa	Ping Kun Liu et al., 2018 [22] Xu Dong Hu et al., 2018[23]
Pectic polysaccharides	Apple and citrus	Yissel et al., 2018 [24]
Black chokeberry fruit	Polyphenols	Sosnowsk; Podsędek &Redzynia, 2018 [25]
N-Phthaloyl	Phenacyl esters of amino acids	Sankar & Engels, 2018 [26]
Phaffia rhodozyma	Astaxanthin	Xiping Du et al., 2018 [27]
Cocoa	Beans (flavan-3-ol)	Stanley et al., 2018 [28]
Dendrobium formosum	Whole plant (phenolic)	Inthongkaew et al., 2017 [29]
1-benzil-3,4-di-hidroisoquinolinas	Synthesized by Bischler-Napieralski cyclization	Tian et al., 2016 [30]

Table 3: Drugs and adjuvants for the treatment of obesity

Study Targets	Function with antiobesity agent	References
Melanocortin	Central nervous system regulator viamelanocortin-4 pathway (MC4Rs)	Kühnen et al., 2019 [40]
Orlistat, lorcaserin, phentermine/topiramate, liraglutide, naltrexone/bupropion	Lorcaserim, Phentermine/topiramate Liraglutide- appetite suppressants	Pilitsi et al., 2019 [41]
Linifanib	To attenuate differentiation of brown adipocytes by attenuating phosphorylation.	Zhao et al., 2019 [41]
Glucocorticoids	Reduction of body weight	Delaleu et al., 2019 [43]
Lorcaserin, phentermine/topiramate, naltrexone/bupropion and liraglutide	Naltrexone/bupropion- decreased appetite	Kushner, 2018 [44]
Metformin, inositol, liraglutide, Orlistat	Metformin- weight reduction inositol	Wang et al., 2018 [45]
Glucagon-like peptide- 1 receptor agonists, Phentermine-topiramate, Lorcaserin, metformin	Glucagon-like peptide- 1 receptor agonists- Appetite suppressants	Grandone et al., 2018[46]
Orlistat	Pancreatic lipase inhibitor	Sahebkar et al., 2017 [47]
Diethylpropion, Phentermine, Orlistat, Lorcaserin, Liraglutide,Naltrexone/Bupropion	Appetite suppressants	Keith, 2016 [48]
Metformin	Reduction of body weight	Kim et al., 2016[49]

Table 4: Alternative natural treatments for obesity treatment using plants

Target of study	References
Phytochemical of plants	Sravani et al., 2019 [1]
Fibers	Patel, 2019 [56]
Leopoldia comosa (L.)	Marreli et al., 2019 [57]
Herbs	Hanieh-Sadat Ejtahed et al., 2019 [58]
Trigonellafoenum-graecum	Cheng et., 2018 [59]
Flavanols	Engin et al., 2018 [60]
Antocianins	Lianghua et al., 2018 [61]
Cagaita fruit (*Eugenia dysenterica* DC.)	Pestana et al., 2018 [62]
Cornus mas L. & *Cornus alba* L.	Swierczewska et al., 2018 [63]
Macrotyloma uniflorum	Bharathi et al., 2018 [64]
Prebiotics	Delgado et al., 2018 [65]
Pectic polysaccharides	Aguilera-Angel et al., 2018 [66]
Methylxanthines	Carrageta et al., 2018 [67]
Diaporthe arengae	Mohini et al., 2017 [68]
Heaflavins	Glisan et al., 2017 [69]
Cyclopia intermedia	Jack et al., 2017 [70]
Moringa oleifera	Metwally et al., 2017 [71]

Table 5. Studies using pancreatic lipase inhibitors from fruit pomace.

Target of study	References
Raspbarry	Fotschkiet al., 2019 [72]
Tomato	Zhiqiang et al., 2019 [73]
Açai	Silva et al., 2018 [74]
Grape seed	Mohamed et al., 2018 [75]
Grape seed	Ruifang et al., 2019 [76]
Blueberry	Hoskin et al., 2019 [77]
Guava	Cerio et al., 2017 [78]
Pomegranate	Yu et al., 2017 [79]

Apple	Madrera et al., 2017 [80]
Grape Merlot	Gonçalves et al., 2017 [81]
Wine pomace	Rosenzweig et al., 2017 [82]
Rapeseed pomace	Franziska et al., 2018 [83]
Blackberry	Chang et al., 2016 [84]

Table 6. Descriptors and numbers of patents in Espacenet database.

Descriptors	**Number of patents (2016)**	**Number of patents (2019)**
Treating obesity	10,000	10,000
Antiobesity agents	219	248
Lipase inhibitor	640	699
Fruit extract	9,961	10,000
Fruit waste	2,100	3,656
Fruit extract and obesity	74	125
Polyphenols	3,705	5,517
Polyphenols and obesity	20	29
Total	26,719	30,274

