NVEO
Natural Volatiles & Essential Oils

A Mechanistic Review of Anti-Obesity Drugs

Nitheesh Kumar[1], Narayanan J[2*], Chitra V[3]

[1]Department of Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu District-603203, Tamilnadu, India.

[2*]Assistant Professor, Department of Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu District-603203, Tamilnadu, India.

[3]Dean and Professor & Head, Department of Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu District-603203, Tamilnadu, India.

Abstract

Obesity is a complicated disease, characterized by an immoderate amount of fat in a human body. Obesity is not alone a point of concern from a cosmetic sector, also affect health problems. The different factor involves in obesity such as genetic factor, environment factor, energy balance dysregulation, metabolic factor. It can be determined by Body Mass Index as well as Body Adiposity Index value and can be controlled by different methods like drugs and nature compounds. This paper reviews on the Food and Drug Administration approved drugs for obesity recently like Semaglutide, bupropion naltrexone, liraglutide, lorcaserin, orlistat, and phentermine topiramate. The natural compounds Salvia officinalis (Lamiaceae), Vitis vinifera (Vitaceae), Arachis hypogaea (Fabaceae), Panax japonicus (Araliaceae).

Keywords: Antiobesity, Arachis Hypogaea, BMI, Bupropion, Phentermine Topiramate.

Introduction

Obesity is becoming one of the most frequent health issues worldwide, resulting in a significant increase in mortality and morbidity from heart disease, type-2-diabetes mellitus, metabolic disease, stroke, and cancer across all ethnicities and age categories.[1] Obesity and overweight prevalence, as well as associated disorders, are key concerns for global health systems, therefore prevention and treatment are critical. Physicians and other health care professionals have investigated both lifestyle and pharmacological therapies as obesity treatment options.[2]

The "obesity epidemic" has recently become one of the most pressing global health issues. Obesity increased globally between 1975 and 2016, with high-calorie diets and sedentary lifestyles being the primary causes.[3]

Obesity and without physical causes undoubtedly different risk factors that both cause illness & death on a worldwide. Obesity and sedentary behavior are linked to a high rate of morbidity. When you include in things like missed work days due to illness and greater health-care expenses, it adds up to a significant financial burden. Obesity is determined by body mass index of above 30 kg/m^2.[4]

Because obesity has a variety of etiological and pathological causes, there is no single treatment or medicine that can effectively control the condition. Furthermore, current drugs have failed to lower weight considerably and successfully, prompting continuous and sophisticated research into obesity therapy.[5] One component to focus in identifying antiobesity extracts from compounds derived by remedial plants that are both easily available and have fewer negative effects. However, the bulk of these remedial plants' mode of action for weight loss, as well as the classes of chemicals or active substances responsible for their antiobesity properties, are unknown.[6]

However, in terms of weight reduction, the method of action of most of these medicinal plants is unclear; neither the chemical classes nor the active ingredients components accountable for these plants' anti-obesity actions have been identified.[7] As a result, the focus of this review is on a number of anti-obesity lead molecule found from different of Phyto-chemicals that operate on known therapeutic action and investigated in a number of preclinical and clinical studies in the hopes of developing them into antiobesity drugs, though the majority have yet to reach the commercial market.[8]

Obese patients should follow current treatment recommendations, which include lifestyle changes, increased physical activity, and calorie reduction. If these therapies are ineffective, pharmacotherapy may be tried. The FDA has authorized the following obesity medications such as: bupropion naltrexone, liraglutide, lorcaserin, orlistat, and phenterminetopiramate.[9] However, the high number of side effects still makes them unsuitable for normal clinical use. Obesity's pathophysiology isn't totally understood. It entails significantly more complicated procedures than the passive accumulation of extra fat throughout the body.[10]

Adipocyte hypertrophy and hyperplasia are two ways that adipose tissue (AT) responds to an excess of nutrients quickly and dynamically. Endocrine and metabolic functions are altered as a result of AT alterations in systemic physiology. AT remodeling has been researched in particular to learn more about the relationship between proinflammatory adipocytokines, cytokines, and obesity-related metabolic issues.[11] Macrophages are important since they are the immune cells that cause AT inflammation. Obesity alters macrophage behavior and promotes the production of proinflammatory chemicals such Tumor-necrosis factor, Interleukin-6 (IL6), and Monocyte-chemoattractant protein (MCP1). Anti-inflammatory adipocytokines are also significantly downregulated when adipocytes and macrophages interact. Obesity-related problems affect a variety of organs, increasing the risk of diseases such insulin resistance, type-2-diabetes, heart attack and numerous types of cancer.[12]

BMI and Body Adiposity Index

The BMI is a measurement of weight in relation to height. Because it cannot distinguish between obesity generated by an excess of fat and obesity induced by an excess of lean mass, the BMI is a poor instrument. BMI, on the other hand, requires accurate scales to calculate. Calculations for children and teens must be adjusted for their age. Furthermore, in those with a high proportion of muscle to fat, BMI may have little bearing on body fat %, resulting in athletes with a high BMI but a low body fat percentage.[13] The body adiposity index (BAI) is an alternative to the BMI (BAI). The BAI has a direct link to body fat percentage and may be used by a wide spectrum of persons. The BAI has not been widely adopted due to the challenges in measuring hip circumference and the lack of historical background.[14]

Epidemiology

Approximately 30.0% of the global population is overweight or obese at this time. According to predictions, more than 60.0% of the world population would be overweight/obese by 2020. According to predictions, the prevalence of severe obesity will reach 11.0% in 2030, over double today's percentage. When a person's BMI surpasses 30, their genetic reset emerges as a resistance to weight reduction, and if they continue to gain weight, they will reach a point where they can no longer lose weight.[15] Amplification of the genetic reset is a dangerous issue for the patient since it greatly impacts the patient's

capacity to repair or control excessive obesity. According to a study, those with a BMI of 40 or above grow the fastest and are at the most risk of obesity-related diseases.[16]

Pathophysiology of Obesity

Environment Factor:

As a result of widespread environmental changes during the previous century, chronic diseases and obesity have become important public health concerns. Infectious illnesses, which were the leading cause of mortality in 1900, are now mostly under control, and Americans' average longevity has grown by nearly three decades. In recent decades, increased per capita food supply and consumption, particularly of high-calorie, appealing meals given in big quantities, have aided in maintaining a positive energy balance and weight gain[17]. The basis for the chronic illness and obesity epidemics was laid in concert with medical advances that lowered infectious disease mortality and extended life expectancy.[18]

Genetic factor:

Epigenetic regulation of genes via methylation, histone modifications, chromatin remodelling, and noncoding RNA changes is one of the biological mechanisms involved in early-life metabolic programming. Importantly, such epigenetically determined increased adult obesity risk can be passed down to future generations, hastening the obesity epidemic even more.[19] Obesity research focuses on developing tools and treatments to interrupt the epigenetic programming cycle. Given the disproportionally high expression of obesity-related genes and epigenetic modifications in the central nervous system, obesity genes are likely to act not only within the hypothalamic homeostatic regulator of energy balance, but also within neural circuits involved in interactions with an obesogenic environment, such as reward-based decision making, learning and memory, delayed discounting, and spatial orientation.[20]

Energy-Balance Dysregulation:

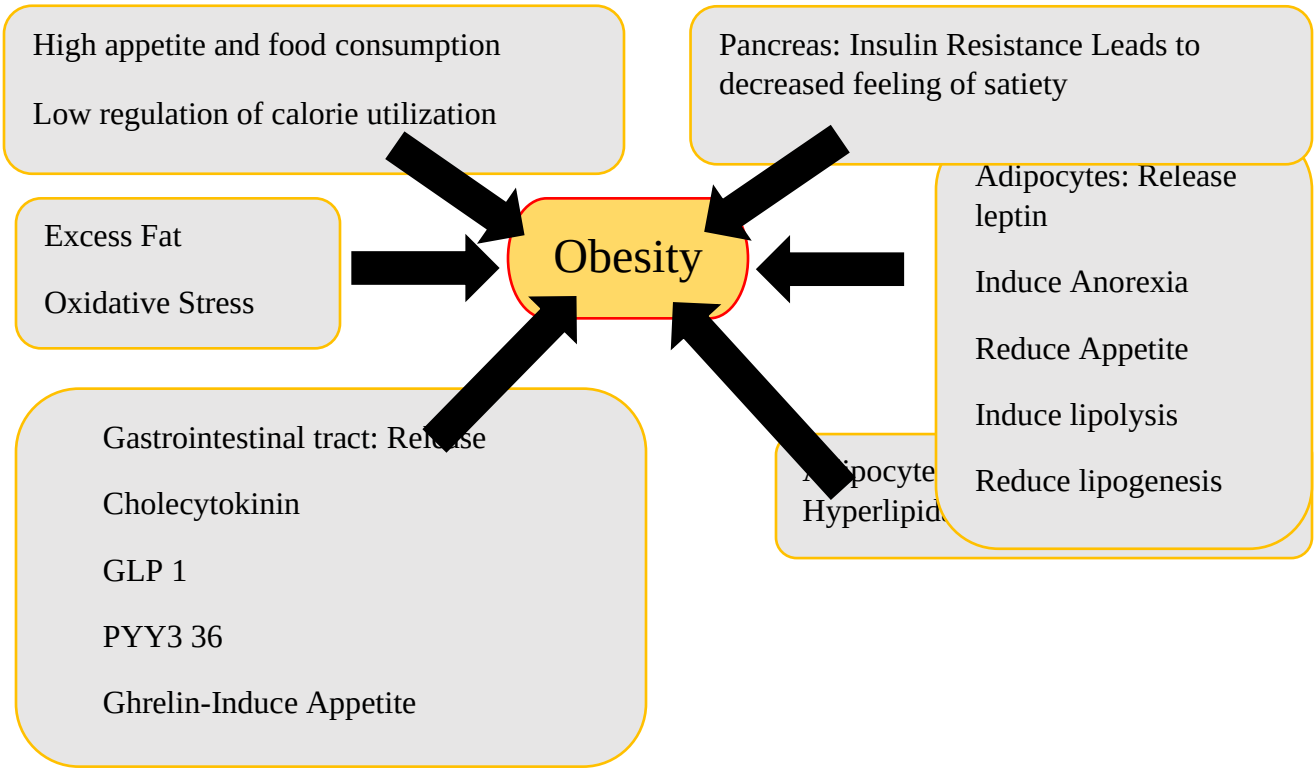
In a complex system, genes and the environment interact to govern energy balance, associated physiological processes, and weight. Circulating neuropeptide hormones block or activate two groups of neurons in the hypothalamic arcuate nucleus, which regulate energy balance through regulating food intake and expenditure. The microbiota and cells in adipose tissue, the stomach, the pancreas, and other organs control short- and long-term energy balance through a coordinated network of central activities and peripheral signals. 14 brain regions contribute to energy balance control outside of the hypothalamus.[21]

Metabolic Effects

Effects on Physiology and Metabolism The volume and location of adipose tissue influences adipocytes generate adipokines (cell signalling proteins) and hormones, which are secreted at different rates and have different effects. Increased production of pro-inflammatory adipokines by adipocytes and macrophages inside adipose tissue causes a low-grade systemic illness in certain obese people. Adipocytes create free fatty acids by hydrolysing triglycerides, which are then delivered via the circulation to metabolic regions where they may be utilised.[22] Obese patients have higher plasma free fatty acid levels, which can be caused by a number of reasons, including an increase in adipose tissue mass. Lipids are present in liposomes, which are tiny cytoplasmic organelles located near the mitochondria in many types

of cells, including adipose tissue. Excess adiposity causes liposomes in hepatocytes to grow (steatosis), resulting in massive vacuoles that are non-alcoholic fatty liver disease, steatohepatitis, and cirrhosis are among the clinical conditions connected to it.[23]

Fig 1: Pathophysiology of Obesity



Excess lipid intermediates can be collected in non-adipose tissues (e.g., ceramides), resulting on lipotoxicity, cellular dysfunction, and death. Insulin signalling is disturbed in non-adipose tissues due to increased amounts of free fatty acids, inflammatory cytokines, and lipid intermediates, resulting in the insulin-resistant condition seen in many overweight or obese patients. An excess of intraabdominal adipose tissue is also connected to insulin resistance.[24]

Obesity-related dyslipidaemia, type-2-diabetes mellitus, metabolic disease, stroke, and cancer are all caused by this constellation of metabolic and anatomical findings. Some malignancies have been linked to increased biological available levels of insulin-like growth factor and other tumour-promote chemicals.[25]

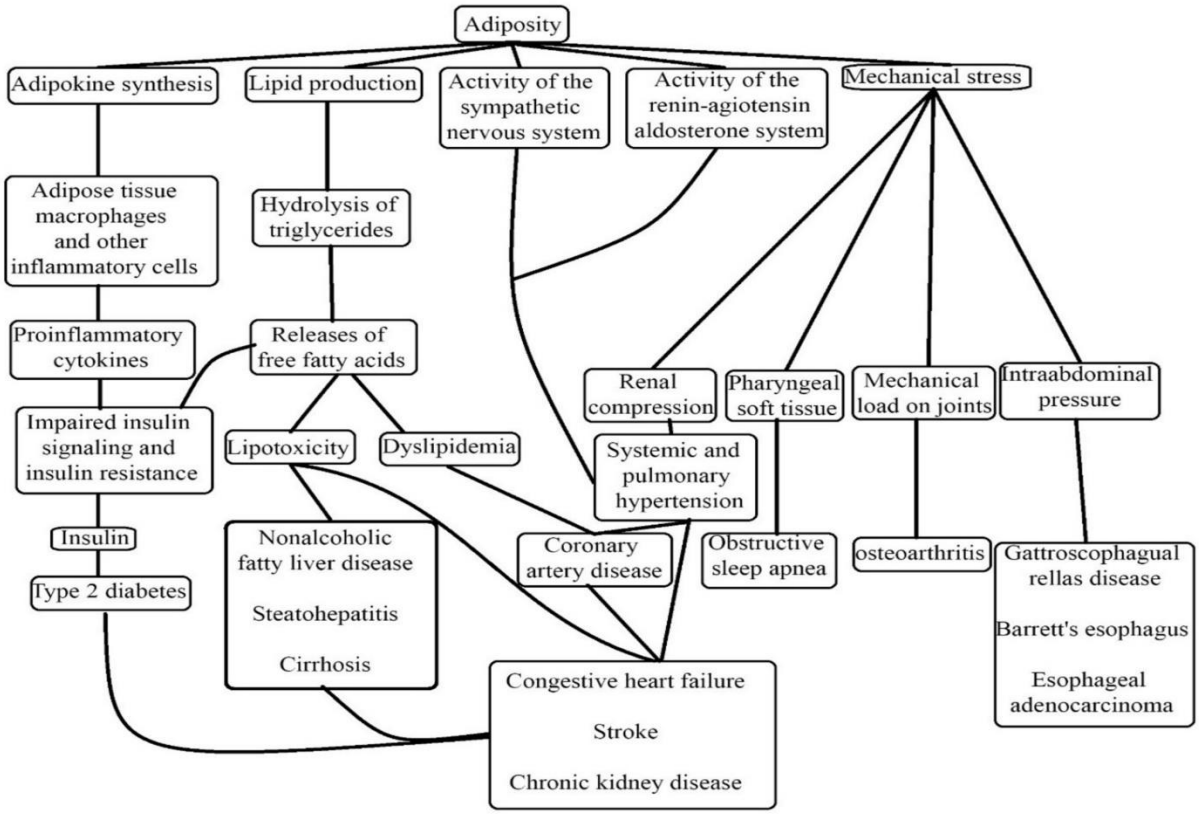
On some fat people, the sympathetic nervous system is overactive persons and is considered to have a role in a range of pathophysiological processes, including high blood pressure. High blood pressure and a cluster of outcomes linked to insulin resistance, obesity-associated dyslipidemia, and type 2 diabetes are the primary pathophysiological mechanisms in heart disease, stroke, and chronic kidney disease. According to this graphic, the mechanical, metabolic, and physiological impacts of excessive adiposity contribute to chronic diseases.[26]

Antiobesity Medications Currently on the Market and their Mechanisms of Action:

Increased energy expenditure, appetite suppression, digestive enzyme blockage, and difficulty with fat or sugar absorption from meals are all symptoms of this condition. at the intestinal tract level are all approaches used by antiobesity drugs. To date, incorrect beginnings, clinical development failures, medical prescription limitations, and withdrawals owing to undesirable effects have been associated to antiobesity prospects. The current Anti-obesity medications have been approved by the FDA are highlighted, as well as their mechanisms of action. Candidate antiobesity pharmaceuticals or antiobesity drug candidates must be able to maintain or lose weight with the fewest possible negative effects.[27]

Orlistat is a lipase inhibitor in pancreas that reduces diet fat absorption by inhibiting lipase activity in the small intestine. Although orlistat does not provide considerable weight reduction, it does help to decrease LDL fat, high cholesterol, and high triglyceride. Orlistat's adverse effects include bloating, diarrhea, gas, and stomach discomfort. In diabetic individuals, a glucagon-like peptide-1-receptor (GLP-1-R) agonist, liraglutide, is found to consistently promote moderate weight reduction. Despite its adverse effects, which include nausea, vomiting, and hypoglycemia, liraglutide causes weight reduction of around 8 kg or more in the treatment of obesity. The FDA has withdrawn or cancelled the FDA licenses for the appetite suppressants rimonabant.[28]

Fig 2: Mechanisms of Action Anti-Obesity



Efficacy of Currently Approved Obesity Therapies:

Orlistat:

Orlistat is an FDA and EMA-approved selective inhibitor of pancreatic lipase that moderates fat breakdown and absorption in the stomach. It is available in the UK in smaller dosages via prescription and over-the-counter, and should be taken with meals. BMI of 30 kg/m^2 people have risk factors are administered orlistat (such as hypertension, diabetes, or hyperlipidemia). While orlistat users lose an extra 3–3.5 kg in a year, gastrointestinal side effects, decreased fat-soluble vitamin absorption, and steatorrhea are also typical adverse effects. In a recent comprehensive study, orlistat usage was connected to a weight reduction of 3.1 kg. Orlistat usage is linked to lower BP (systolic, 1.15 millimeters of mercury; diastolic, 1.07 millimeters of mercury) and circulating lipids (total cholesterol, 0.30 millimeters of mercury; low-density lipoprotein (LDL) cholesterol, 0.27 millimeters of mercury; triglycerides, 0.09 millimeters of mercury According to one study, the price of orlistat fat loss per kilogram was US$546, with each quality-adjusted life year (QALY) costing US$71,000 in Europe.[29]

Phentermine/Topiramate

Topiramate is a kind of anticonvulsant that aids in weight loss when they take phentermine, while the exact mechanism of appetite reduction is unknown. Topiramate is an anticonvulsant that which used for people lose weight when they take phentermine, while the exact mechanism of appetite reduction is unknown. Topiramate used with phentermine, though the mechanism to decreases food intake by lowering the stimulation appetite. Phentermine is a sympathomimetic that increases noradrenaline release, decreases appetite. It is a useful in weight-reduction medicine, for 12-month weight loss of 7-8 kg reported in trials. In randomized-controlled studies, it resulted in an average weight loss of 10 kg, according to a more recent meta-analysis. Insomnia, dizziness, and paresthesia are some of the negative effects. Despite the FDA's clearance in 2012, the European Medicines Agency (EMA) has banned its usage due to safety concerns. The cost of taking topiramate is discovered to be US high one very kilogram of fat reduction.[30]

Lorcaserin:

Lorcaserin is an appetite suppressant that acts by activating hypothalamic 5-HT2C receptors. It was authorized by the FDA in 2012. It's for those have a BMI of 30 kg/m^2 or 27 kg/m^2 who have co-morbidities (Hypertension, diabetes, and dyslipidemia are examples of such conditions.). Lorcaserin usage is connected to a 3.2–3.6 kg weight reduction per year, Furthermore, metabolic indicators such as blood-pressure levels both improved. A systematic evaluation of randomized controlled studies found that locaserin caused a 3.1 kg weight reduction on average. Headache, nausea, and dizziness are all frequent lorcaserin side effects. According to research, the cost of this therapy is $545 every kilogram decreased.[31]

Bupropion:

Bupropion is an opiate antagonist, whereas naltrexone is a dopamine and noradrenaline re-uptake inhibitor with a moderate potency. The “FDA” and the European Medicines Agency have approved it for the treat for obesity. These drugs operate synergistically to increase the release of melanocyte stimulating hormone (MSH) from hypothalamic proopiomelanocortin cells, resulting in food intake is lower, and

energy expenditure is higher. Like other obesity drugs, naltrexone/bupropion is licenced for BMI C 30 kg/m^2 or C 27 kg/m^2 when used in conjunction with other obesity-related co-morbidities. A total body fat reduction of 5.0% percent was seen annually, nausea being one of the adverse effects. Annually, an additional 5.0% total body fat loss (mean 4.4 kg) was seen with nauseousness, headache, and dizziness as side effects.[32]

Liraglutide:

Liraglutide is a GLP-1 agonist that is developed to treat diabetes (Type-2). It is administered as a daily injection at once with 3.0 mg. Liraglutide improves body fat loss by increasing satiety and lower energy loss and appetite, leading in a reduction in food intake. The FDA and EMA have approved it to help people lose weight who have a BMI of more than 30 kg/m^2 with obesity related comorbidities. Nausea/vomiting and pancreatitis are the most common side effects. When compared to the placebo, an additional 5.3–5.9 kg of weight loss per year was observed.[33]

Semaglutide:

Semaglutide is GLP-1 agonist that is given once a week. It was initially authorised in 2017 under the trade name Ozempic to assist manage blood sugar in type 2 diabetes at a significantly lower dose. As a side effect of using Ozempic for blood sugar management, people tend to lose weight. As a consequence, Novo Nordisk tried the medication at a higher dose in people who did not have type 2 diabetes. The FDA has officially authorised semaglutide (marketed as Wegovy) for weight loss in those with a BMI of more than or equal to 30 mg/kg^2 alone or 27 mg/kg^2 with at least one weight-related comorbidities (e.g., high blood pressure, high cholesterol). Semaglutide should be taken in conjunction with other lifestyle modifications including eating a healthy diet and exercising regularly.[34]

Natural product for antiobesity:

Salvia officinalis (Lamiaceae):

Salacia reticulata roots and stems have been used as a supplemental meal to help people avoid obesity and diabetes. Obese models of rat and an invitro investigation were used to assess the antiobesity activities of e extract of S. reticulata roots it soluble only in boiled water. In vitro, SRHW dramatically reduced pancreatic lipase. It also stopped mice from gaining weight when they were fed a high-fat diet. S. reticulata root contain polyphenols, diterpenes, triterpenes, and salacinol which contain antiobesity characteristics of S. reticulata when their effects on lipid metabolizing activity and lipolysis were investigated.[35]

Table 1: Drug with mechanism and adverse effect

Vitis vinifera (Vitaceae):

Compound	**Mechanism**	**Adverse effect**
Orlistat	Lipase inhibitor	Steatorrhea, Flatulence
Liraglutide	Glucagon-like peptide-1-receptor agonist	Diarrhea, nausea, vomiting, hypoglycemia, and constipation are all symptoms of diabetes.
Lorcaserin	5-HT2C receptor agonist	Nausea, dizziness, and headaches are common side effects.
Bupropion	Dopamine and noradrenaline reuptake inhibitor and opioid receptor antagonist.	Some of the symptoms include nausea, headaches, vomiting, dizziness, constipation, and dry mouth.
Topiramate	Synaptic NA, serotonin, and dopamine-release stimulator, as well as y-aminobutyrate activity stimulator	Dry mouth, constipation, sleeplessness, and dizziness are all symptoms of paresthesia.
Semaglutide	Incretin inhibitors, GLP-1 agonists	Constipation, stomach pain, Headache, Fatigue

Grape polyphenols, which are derived from seeds of grape and are commonly add of diet, are now being studied to discover if they offer any health benefits. Grape seed extract high in proanthocyanidins has been confirmed to have minimal toxicity in several studies, indicating that it may be utilized in a range of diets.[36] Grape Seed Extract, which contain high in biologically active phytochemicals, inhibited the fat enzymes lipoprotein lipase and pancreatic lipase, indicate it may be used to reduce dietary fat absorption and adipose tissue fat storage. Reduced intra-cellular activity in cultured of adipocytes might lead to decreased amounts of free fatty acids in circulation, which associated to obesity-related insulin deficiency. Rather than a single component, the impact of Grape Seed Extract on lipase may be attributable to the induce activity of many chemicals inside the extract. These procyanidins, flavonoids, and their antioxidative metabolites may be used to the prevention of obesity.[37]

Arachis hypogeal:

Hypoglycemic and hypolipidemic properties have been discovered in Arachis hypogaea. In male wistar rats, the extract has also been demonstrated to inhibit body weight increase caused by a high-fat diet. Many biological active components of pea nut shell (PSE)extract is likely to have caused these effects. Due to its metabolic complexity, the extract may have a pleiotropic impact on many lipids' metabolism sites at

the same time. As a result, PSE looks to be a best candidate for a new fat-loss medicine with several functions.[38]

Scabiosa tschiliensis (Dipsacaceae):

As an herbal medicine, S. tschiliensis has historically been used to treat headaches, fevers, coughs, and yellow fever. An extract of the full plant significantly lower lipase activity in pancreas. Hookeroside A, hookeroside B, prosapogenin, Scabiosaponin E, Scabiosaponin F, Scabiosaponin G, and Scabiosaponin I, were shown to inhibit lipase in in invitro one of the numerous triterpenoids and saponins extract of the plant.[39]

Panax japonicus (Araliaceae):

P. japonicus rhizomes are used Ginseng root replacement. Ginseng roots are utilized in some countries like Japan, China, Korea, and Europe to treat lifestyle problems such coronary diseases, hyper-lipidemia, high blood pressure, and non-insulin dependent diabetic. The saponin present in rhizomes of P. japonicus have been revealed to have an anti-obesity effect, proving its traditional use. Pancreatic lipase is inhibited in vitro by the active ingredients chikusetsusaponins III and IV, as well as deglucosyl-chikusetsusaponins IV and V. Total isolated from P. japonicus may help to reduce weight gain and fat accumulation caused by a high-fat diet in adipose tissue by reducing intestinal absorption of dietary fat via reduced pancreatic lipase activity. As a result, it may be useful as an adjuvant in the current arsenal of antiobesity drugs, helping to avoid obesity disorders.[40]

Prevention and Treatment Mechanisms:

Obesity is a disease that develops as a result of a person's behaviour as well as the environment in which they live. As a result, both mandatory and volunteer counselling programmes to help people prevent getting fat are available. Obesity can be avoided or managed by following the steps mentioned below.

Nutrition Education:

The purpose of interventional research named "Healthy Primary School of the Future" is to decrease children's BMI z-scores by focusing health education, a healthy eating strategy, and physical exercise programmes during lunch. Another Brooklyn initiative, “Live Light, Live Right" was a lifestyle that includes a health evaluation, dietary guidance, access to physical activity programmes, and behavioral changes to lower BMI Z-Scores. Even a small amount of physical activity can help pregnant women avoid becoming overweight or obese.[41]

Creating a plan for a nonsedentary lifestyle:

Physical activity, reduced inactivity, decreased fast food intake, 8 hours of sleep, no smoking, and less alcohol use are all recommended use have all been demonstrated to be effective obesity treatments.[42]

Subsidies for healthy foods and taxes on food that is unhealthy:

Subsidizing healthy meals and charging taxes on unhealthy foods, the government may assist individuals in losing weight. This is often used in the United Kingdom; this scenario shows how a 20% rise

in the price of high-sugar snacks leads to a significant reduction in calorie consumption, BMI, and obesity prevalence.[43]

Conclusion:

Obesity is a complex disease which leads to several other diseases such as heart attack, blood pressure, etc. In this review we summarized the drugs involved in the treatment and management of obesity through which we can understand the current medication involved in the regimen. In addition to that, the pathogenesis described here, helps in better understanding of the disease which paves a way for developing advance treatment.

ACKNOWLEDGEMENTS:

We thank Prof.V. Chitra, M.Pharm., Ph. D., Dean, SRMIST College of Pharmacy and staff for providing necessary guidance for this review to be successful.

DECLARATIONS:

Ethics approval and consent to participate: Not applicable.
Consent for publication: Not applicable.
Availability of data and material: All data and material are available upon request.
Funding: No funding received

REFERENCES:

1. Williams DM, Nawaz A, Evans M. Drug Therapy in Obesity: A Review of Current and Emerging Treatments. Diabetes Ther . 2020;11(6):1199–216.
2. Wolfenden L, Ezzati M, Larijani B, Dietz W. The challenge for global health systems in preventing and managing obesity. Obesity Reviews. 2019 Nov;20:185-93.
3. Malenfant JH, Batsis JA. Obesity in the geriatric population–a global health perspective. Journal of global health reports. 2019;3.
4. Lavie CJ, Laddu D, Arena R, Ortega FB, Alpert MA, Kushner RF. Healthy weight and obesity prevention: JACC health promotion series. Journal of the American College of Cardiology. 2018 Sep 25;72(13):1506-31.
5. Jindal A, Thadi A, Shailubhai K. Hepatocellular carcinoma: etiology and current and future drugs. journal of clinical and experimental hepatology. 2019 Mar 1;9(2):221-32.
6. Lankatillake C, Huynh T, Dias DA. Understanding glycaemic control and current approaches for screening antidiabetic natural products from evidence-based medicinal plants. Plant Methods. 2019 Dec;15(1):1-35.
7. Saad B, Zaid H, Shanak S, Kadan S. Anti-diabetes and anti-obesity medicinal plants and phytochemicals. Anti-diabetes and Antiobesity Medicinal Plants and Phytochemicals. 2017.
8. Egbuna C, Kumar S, Ifemeje JC, Ezzat SM, Kaliyaperumal S, editors. Phytochemicals as Lead compounds for new drug discovery. Elsevier; 2019 Sep 7.
9. Lee PC, Dixon J. Pharmacotherapy for obesity. Australian family physician. 2017 Jul;46(7):472-7.
10. Bertsch T, Erbacher G, Elwell R, Partsch H. Lipoedema: a paradigm shift and consensus. Journal of Wound Care. 2020 Nov 1;29(Sup11b):1-51.

11. Santoro A, McGraw TE, Kahn BB. Insulin action in adipocytes, adipose remodeling, and systemic effects. Cell Metabolism. 2021 Apr 6;33(4):748-57.
12. Parisi L, Gini E, Baci D, Tremolati M, Fanuli M, Bassani B, et al. Macrophage polarization in chronic inflammatory diseases: killers or builders?. Journal of immunology research. 2018 Oct;2018.
13. Olfert MD, Barr ML, Charlier CM, Famodu OA, Zhou W, Mathews AE, Byrd-Bredbenner C, Colby SE. Self-reported vs. measured height, weight, and BMI in young adults. International Journal of Environmental Research and Public Health. 2018 Oct;15(10):2216.
14. Zwierzchowska A, Celebańska D, Rosołek B, Gawlik K, Żebrowska A. Is body mass index (BMI) or body adiposity index (BAI) a better indicator to estimate body fat and selected cardiometabolic risk factors in adults with intellectual disabilities?. BMC Cardiovascular Disorders. 2021 Dec;21(1):1-7.
15. Tang J, Zhou Q, Nie B, Hu J. Obesity effects on pedestrian lower extremity injuries in vehicle-to-pedestrian impacts: A numerical investigation using human body models. Traffic injury prevention. 2020 Oct 22;21(8):569-74.
16. Toomath R. The Obesity Epidemic: Why Diets and Exercise Don't Work—and What Does. JHU Press; 2017 Feb 28.
17. Raghupathi W, Raghupathi V. An empirical study of chronic diseases in the United States: a visual analytics approach to public health. International journal of environmental research and public health. 2018 Mar;15(3):431.
18. Gutin I, Hummer RA. Social Inequality and the Future of US Life Expectancy. Annual Review of Sociology. 2021;47.
19. Bianco-Miotto T, Craig JM, Gasser YP, van Dijk SJ, Ozanne SE. Epigenetics and DOHaD: from basics to birth and beyond. Journal of developmental origins of health and disease. 2017 Oct;8(5):513-9.
20. Han JC, Weiss R. Obesity, Metabolic Syndrome and Disorders of Energy Balance. InSperling Pediatric Endocrinology 2021 Jan 1 (pp. 939-1003). Elsevier.
21. Mancuso P, Bouchard B. The impact of aging on adipose function and adipokine synthesis. Frontiers in endocrinology. 2019 Mar 11;10:137.
22. Ghaben AL, Scherer PE. Adipogenesis and metabolic health. Nature reviews Molecular cell biology. 2019 Apr;20(4):242-58.
23. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. New England Journal of Medicine. 2017 Jan 19;376(3):254-66.
24. Ahmed B, Sultana R, Greene MW. Adipose tissue and insulin resistance in obese. Biomedicine & Pharmacotherapy. 2021 May 1;137:111315.
25. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. New England Journal of Medicine. 2017 Jan 19;376(3):254-66.
26. Saliba LJ, Maffett S. Hypertensive heart disease and obesity: a review. Heart failure clinics. 2019 Oct 1;15(4):509-17.
27. Meneguetti BT, Cardoso MH, Ribeiro CF, Felício MR, Pinto IB, Santos NC, et al. Neuropeptide receptors as potential pharmacological targets for obesity. Pharmacology & therapeutics. 2019 Apr 1;196:59-78.
28. Xuan YU, Xin-Pei WA, Fan LE, Jiang JF, Jun LI, Dong-Ming XI, et al. Pomegranate leaf attenuates lipid absorption in the small intestine in hyperlipidemic mice by inhibiting lipase activity. Chinese journal of natural medicines. 2017 Oct 1;15(10):732-9.

29. Luo S, Lenon GB, Gill H, Yuen H, Yang AW, Hung A et al. Do the natural chemical compounds interact with the same targets of current pharmacotherapy for weight management?-A review. Current drug targets. 2019 Mar 1;20(4):399-411.
30. Verhaegen AA, Van Gaal LF. Drugs that affect body weight, body fat distribution, and metabolism. Endotext [Internet]. 2019 Feb 11.
31. Chaudhry S. Pharmacotherapy in Obesity. IP International Journal of Comprehensive and Advanced Pharmacology. 2020 Oct 15;5(3):110-7.
32. Patel DK, Stanford FC. Safety and tolerability of new-generation anti-obesity medications: a narrative review. Postgraduate medicine. 2018 Feb 17;130(2):173-82.
33. Lee S, Lee DY. Glucagon-like peptide-1 and glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes. Annals of Pediatric Endocrinology & Metabolism. 2017 Mar;22(1):15.
34. Klyver PG, Hunt TR, Malkin SJ. Management of Patients with Type 2 Diabetes with Once-Weekly Semaglutide Versus Dulaglutide, Exenatide ER, Liraglutide and Lixisenatide: A Cost-Effectiveness Analysis in the Danish Setting.
35. Saad B, Zaid H, Shanak S, Kadan S. Anti-diabetes and anti-obesity medicinal plants and phytochemicals. Anti-diabetes and Antiobesity Medicinal Plants and Phytochemicals. 2017.
36. Ma ZF, Zhang H. Phytochemical constituents, health benefits, and industrial applications of grape seeds: A mini-review. Antioxidants. 2017 Sep;6(3):71.
37. Weseler AR, Bast A. Masquelier's grape seed extract: From basic flavonoid research to a well-characterized food supplement with health benefits. Nutrition journal. 2017 Dec;16(1):1-9.
38. Hernández-Alonso P, Camacho-Barcia L, Bulló M, Salas-Salvadó J. Nuts and dried fruits: an update of their beneficial effects on type 2 diabetes. Nutrients. 2017 Jul;9(7):673.
39. Wang R, Hu X, Agyekumwaa AK, Li X, Xiao X, Yu Y. Synergistic effect of kojic acid and tea polyphenols on bacterial inhibition and quality maintenance of refrigerated sea bass (Lateolabrax japonicus) fillets. LWT. 2021 Feb 1; 137:110452.
40. Bhardwaj M, Yadav P, Vashishth D, Sharma K, Kumar A, Chahal J, et al. A review on obesity management through natural compounds and a green nanomedicine-based approach. Molecules. 2021;26(11):1–28.
41. Bartelink NH, van Assema P, Kremers SP, Savelberg HH, Oosterhoff M, Willeboordse M, et al. Can the Healthy Primary School of the Future offer perspective in the ongoing obesity epidemic in young children? A Dutch quasi-experimental study. BMJ open. 2019 Oct 1;9(10): e030676.
42. Hayes JF, Fitzsimmons-Craft EE, Karam AM, Jakubiak J, Brown ML, Wilfley DE. Disordered eating attitudes and behaviors in youth with overweight and obesity: implications for treatment. Current obesity reports. 2018 Sep;7(3):235-46.
43. Blakely T, Cleghorn C, Mizdrak A, Waterlander W, Nghiem N, Swinburn B, "et al.". The effect of food taxes and subsidies on population health and health costs: a modelling study. The Lancet Public Health. 2020 Jul 1;5(7):404-13.