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OBESITY - A NATURAL CURE- A REVIEW

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Abstract:

As per WHO, Obesity is abnormal or excessive fat accumulation that may impair health. Women are more obese than the men in Gujarat State. Between the age of 15-49 years, 23.7% Women and 19.7% Men are overweight or obese (BMI ≥ 25.0 kg/m2) as per National Family Health Survey - 4, 2016 -17. Obesity leads to Diabetes mellitus, hypertension, and dyslipidemia. There are two major factors (i) Environmental (ii) Genetic, enhance the blood lipid levels. Basic Pathophysiology of obesity indicates insufficiency of Leptin, Ghrelin Hormones or insufficiency of Leptin, Ghrelin the receptors. Current Drug Treatment includes statins, bile acid sequestrants, ezetimibe that have side effects like rhabdomyolysis, muscle complaints, gastrointestinal disturbances, myalgia. Recent targets of the obesity are Amylin analogues, leptin analogues, GLP-1 analogues, Neuropeptide Y antagonists etc., which affects the hormonal balance into the body. Herbal Drugs are same effective as Current treatment, with no significant side effects. They are easily available from the natural sources, bio-compatible, Eco-friendly in nature. Certain edible mulberries, algaes, are the recent herbal sources for the treatment of the obesity.

Key words: *Obesity, BMI, Rhabdomyolysis, Myalgia, Eco-Friendly, Edible mulberries, Algae.*

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INTRODUCTION:

As per WHO, Obesity is abnormal or excessive fat accumulation that may impair health [1]. Women are more obese than the men in Gujarat State. Between the age of 15-49 years, 23.7% Women and 19.7% Men are overweight or obese (BMI ≥ 25.0 kg/m2) as per National Family Health Survey - 4, 2015 -16 [2]. Body mass index (BMI) is used to define obesity. BMI is the ratio of a person's weight in kilograms and the square of his height in meters (kg/m2) [1].

BMI (kg/m2)	Nutritional Status
Below 18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Pre-obesity/ Over weight
30.0–34.9	Obesity class I
35.0–39.9	Obesity class II
Above 40	Obesity class III

BMI is widely used factor, but it does not give the information related to the accumulation of fat in different body locations [3]. Increase in BMI by 5-unit each leads to 34% CVD mortality in men and 29% in women [4]. Higher BMI indicates higher risk of Diabetes mellitus, hypertension and dyslipidemia [5].

Etiology :-

Various factors that are responsible for the obesity, but two major factors are [i] Environmental and [ii] Genetic. others are unusual factors.

i] Environmental factors: - It means external factors which include reduced physical exercise or work; and increased junk food intake; increased fat and simple sugars consumption; and decreased ingestion of balance diet [6].

ii] Genetic factors: - Currently over 430 genes or chromosomal regions have been implicated in the ethology of obesity [6]. Certain gens like MC4R [7,8], FTO [9], and INSIG2 [10], responsible for body fat accumulation and variation.

iii] Physiological factors: - Many neurotransmitters and neuropeptides stimulate or depress the brain's appetite network, impacting total caloric intake [6]. Dopamine receptor deficiency produce obesity [11]{Wang 2001}.

iv] Medical Condition :- Hypothyroidism, Cushing's syndrome, hypothalamic lesion, Prader-Willi's syndrome, Bardet–Biedl Syndrome, BDNF and TRKB Deficiency, SIM1 Deficiency can cause the obesity, but these factors are unusual [6,12].

v] Family: - Family members are having same lifestyle and share diet and food items.

vi] Culture: - Certain cultures have a high lipid and high sugar food intake, which cause obesity [13].

Fig .1 Indicates Etiological circle of Obesity.

Pathophysiology :-

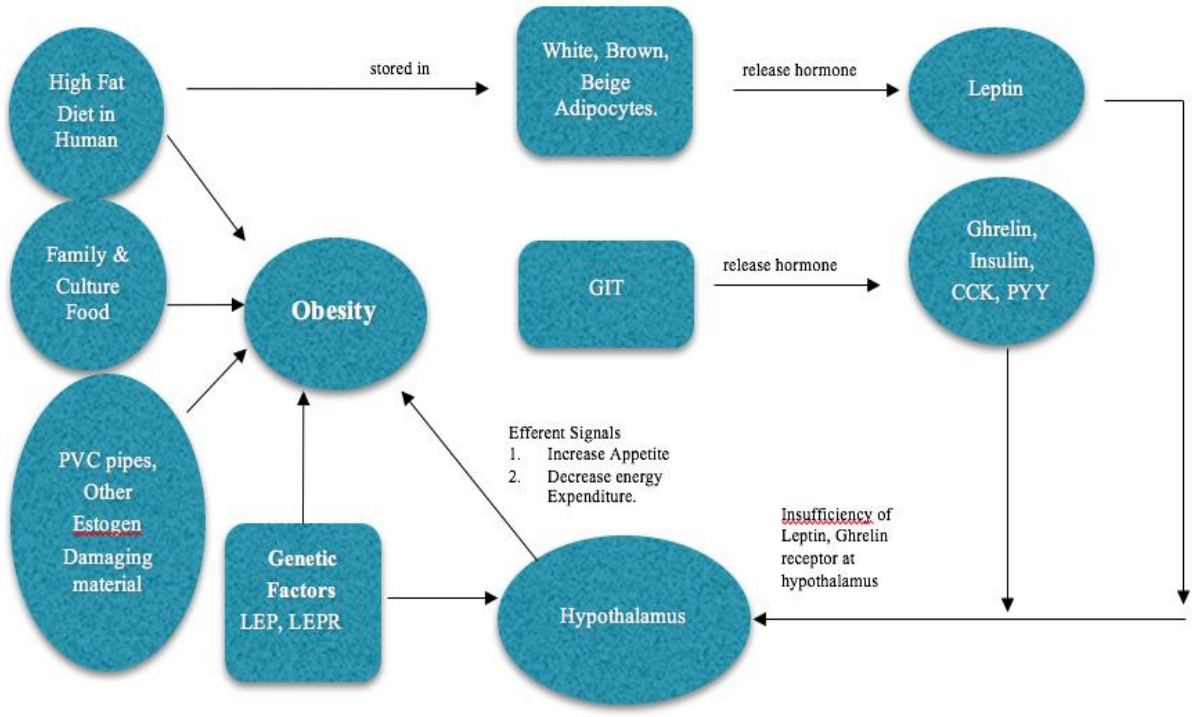
The degree of obesity is determined by the net balance between energy intake and energy expended over time. The Metabolic rate, which is single largest determinant of energy expenditure, expressed as the minimal rate of energy expenditure per unit time by endothermic animals at rest. The two terms are frequently used interchangeably because they differ by less than 10%[14].
Extra Fat and triglycerides are stored into different type adipocytes. Major 3 types of adipocytes,

1) White adipocytes: White adipocytes are the main cell type found in human adipose tissue. Energy-yielding triglycerides and cholesterol ester are stored within the white adipocytes. Leptin, adiponectin, and other adipokines are among the proteins secreted by white adipocytes.
2) Brown adipocytes: Multiple lipid droplets and uncoupling protein 1– containing mitochondria are found within brown adipocytes, which can be activated to produce heat through sympathetic nervous system stimulation after cold exposure.
3) Beige adipocytes: Thermogenic beige or "brite" (brown-and-white) adipocytes are found scattered within white adipose tissue. "Browning" of white

adipose tissue can be induced with cold exposure, exercise, and some endocrine hormones [15].

In non-obese person, weight gain or loss is affects the size of adipocytes but not affects the number of the adipocytes. When, adipocytes reach their maximum size, further weight gain is achieved by proliferation of new pre-adipocytes. Weight loss occurs mainly by a decrease in fat cell size, not the number of adipocytes [16].

leptin is released into the circulatory system by the adipose tissue, After that it crosses the BBB and binds to the hypothalamic receptors. The orexigenic and anorexigenic neurones, which are located in the various hypothalamic regions interact with each other. but after interaction, anorexic effects of the leptin has been shown on to the hypothalamus. Ghrelin peptide was originally isolated from the stomach; leptin induces weight loss by suppression of food intake, whereas ghrelin functions as



an appetite-stimulatory signal. Ghrelin decrease the leptin-induced reduction in food intake and body weight by modulating the expression of various hypothalamic peptides. Ghrelin stimulates the activity of neurones expressing NPY, AgRP and orexin. Disturbance leads to change into net energy level and produce accumulation of excessive fats and cholesterol[17]. Elevations of fasting total cholesterol concentration which may or may not be associated with elevated TG concentration leads to Hyperlipidemia which is major pathogenic factor of Obesity[18]. Genetic factors are the one, which can affects the total cholesterol and fat levels. Mutations in genes encoding leptin and its receptors (LEP, LEPR), situated at hypothalamus, leads to deficiency in leptin sensitivity[19]. POMC deficiency is due to the lack of activation of the melanocortin-4 receptor leads to early-onset obesity. Mutations in melanocortin 4 receptor (MC4R) gene produce juvenile obesity [20]. Higher level of neuropeptide Y (NPY) gene leads to fatty body[21]. Organotin compounds are used as stabilizers in polyvinyl-chloride (PVC) plastic, which is used to manufacture the pipes that carry water into homes, and organotin compounds leach out of PVC into water and leads to obesity[22]. change into food habit and food diet produce obesity, family style and certain cultures have higher food intake[23].Statins, Bile acid Sequestrants, Ezetimibe, are generally used as current therapeutic treatment for the Hyperlipidemia, having adverse effects like Rhabdomyolysis, Gastrointestinal disturbances, Myalgias respectively.

Current Drug Treatment and their side effects [24]:-

Drug	MOA	Example of Drugs & Dose range	Side Effects
STATINS	3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors	Fluvastatin (20-80mg) Pravastatin(10-80 mg) Lovastatin(10–80 mg) Simvastatin(5–80 mg) Atorvastatin (10–80 mg) Rosuvastatin (5–40 mg) Ezetimibe (10 mg)	Abdominal pain, constipation, flatu- lence, nausea, headache, fatigue, diarrhea, and muscle complaints, hypothyroidism, vitamin D deficiency, rheumatologic conditions, Rhabdomyolysis.
Bile acid sequestrants	Increased conversion of cholesterol into bile within the liver	Cholestyramine (4–24 g) Colestipol (5–30gm-powder) (2–16 g-tablet) Colesevelam (3.75–4.38g)(6–7 tablets)	Gastrointestinal disturbances, such as constipation, nausea, bloating, abdominal pain, flatulence, and aggravation of hemorrhoids.
Ezetimibe (10 mg)	Cholesterol absorption inhibitor	(10 mg)	Diarrhea and possibly myalgia

Recent Targets of Obesity [25]:-

Recent Targets of Obesity	Example of Drug
Amylin analogues	Pramlintide, davalintide
leptin analogues	Metreleptin
GLP-1 analogues	Exenatide, liraglutide, TTP-054
MC4R agonists	RM-493
Neuropeptide Y antagonists	Velneperit
Cannabinoid type-1 receptor blockers	AM-6545
Anti-obesity vaccines	Ghrelin, somatostatin, Ad36

Enlisting In Vitro Assays And In Vivo Animal Models [26]:-

In Vivo and In Vitro Animal Model	
In Vitro Assays	**In Vivo Models**
Anorectic Activity (Food Consumption in Rats, Spontaneous Sucrose Drinking, Food Intake in 18-h Fasted Rats)	Food-Induced Obesity
Metabolic Activity (GDP-Binding in Brown Adipose Tissue, Resting Metabolic Rate)	Hypothalamic lesions Obesity
Assays of Obesity-Regulating Peptide Hormones (Determination of Leptin mRNA Level in Adipose Tissue, Determination of Plasma Leptin, Receptor Assay of Neuropeptide Y, Assay of Ghrelin)	Goldthioglucose-Induced Obesity
	Genetically Obese Animals
	Transgenic ANIMALS
	Drug induced obesity

An herbal medicine are playing important role in maintenance of health in rural and remote areas, and provides the health for all. Utilization of Herbal medicine along with conventional drug defiantly promote health or cure diseases in the positive way.[27]

Certain Herbal Drugs with anti obesity Action:-

1) ***Cosmos caudatus Kunth:-*** It also known as 'Ulam raja' in Malaysians. It contains catechin, chlorogenic acid, epicatechin, kaempferol, rutin and quercetin derivatives. It inhibits the activity of Pancreatic lipase (PL) and lipoprotein lipase (LPL). In-vivo study for the effects of C. caudatus leaves' extract on the lipid profile of hyperlipidemia in lean rats fed a high fat diet, it showed that the extract reduced plasma triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), glucose and atherogenic index (AI), and increased high-density lipoprotein (HDL)[28].

2) ***Memecylon umbellatum:-*** This herb, commonly known as Iron wood tree. It contain amyrin, sitosterol, oleanolic acid, ursolic acid, sitosterol - D- glucoside and a new substance umbelactone.[29]oral administration of methanolic extract of MU in DIO mice leads to reduction in body weight, triglycerides and ameliorates insulin resistance[30].

3) ***Zea mays:-*** It is also known as Corn silk. The stigma of *Zea mays* L. has traditionally been used in weight loss. Anthocyanins, quercetin and phenolics acids were the major compositions of purple corn silk. It inhibits on adipocyte proliferation and adipogenesis as well as induction on lipolysis and apoptosis at high concentration[31].

4) ***Taeeumjowuitang (TJ):-*** This is an alternative herbal medicine that has been used to treat obesity in Korea. TJ treatment ameliorated insulin resistance, dyslipidemia, and hepatic steatosis in high-fat diet-induced obese mice. The molecular mechanisms involved in TJ-induced anti-obesity effects have not yet been determined[32].

5) ***Stereospermum suaveolens:-*** It is popularly known as padhri, is a large deciduous tree found throughout the moist parts of India. It contains Cycloolivil, Lapachol and β-sitosterol,[33] and other alkaloids, glycosides, avonoids, saponins,

phenolic compounds, tannins, etc. Administration of Stereospermum suaveolens for 40 days along with HFD decreased the serum concentration of TC, TG, LDL-C and increased the concentration of HDL-C which may be due to lowering lipogenesis, enhancing lipolysis, suppressing appetite and reducing lipid absorption [34].

6) ***Lagenaria siceraria:-*** It is a climber or trailer of Asian and African origin with subglobose ellipsoid or lageniform fruit. The fruit has been found to contain ascorbic acid , caffeoylquinic acid, cucurbitacins, pectin, *β*-carotene, iso-fucosterol, campesterol, spinasterol, kaempferol, palmitic acid, oleanolic acid, linoleic acid, quercetin and iso-quercetin. Fatty acids and their esters may play role as inhibitors of pancreatic lipase. Regular intake of aqueous decoction of the fruit may therefore be recommended for control of obesity [35].

7) ***Moringa oleifera:-*** It is widely cultivated in tropical and subtropical areas. It is commonly known as miracle tree, since various parts of the plant including roots, leaves, and seeds possess various medicinal as well as nutritional values. The methanolic extract of *M. oleifera* leaves improved dyslipidemia and body weight gain in experimentally induced obesity in rats[36]. It Contains vitamins, minerals, amino acids, carotenoids, alkaloids, and flavonoids and contains phenolic compounds, such as zeatin, quercetin, isoquercetin, kaempferol, apigenin and rutin. it suppresses the expression of "LDL scavenger receptors" on macrophages, thus lowering LDL uptake and plaque formation[37].

8) ***Peucedanum japonicum:-*** The Peucedanum japonicum(Apiaceae), comprising more than 120 species, grows across Asia, Africa, and Europe. Several Peucedanum species have been traditionally used for the therapeutic treatments of various conditions. It contains coumarins and essential oils. It is reported that cis-30,40-diisovalerylkhellactone have anti-adipogenic, which is isolated from Peucedanum japonicum[38].

9) ***Viola mandshurica:-*** It is a perennial herb in the family Violaceae that is widely distributed in China, Korea, and Japan. It has traditionally been used in conditions such as bronchitis, eczema, and skin eruptions [39]. Esculetin, schaftoside are the phytoconstituents responsible for activity. It exert anti-obesity effects in HFD-induced obese mice by activating AMPK and suppressing lipid metabolism in adipose tissue and the liver[40].

10) ***Mulberry plants:-*** Genus Morus (Mulberry) is one such example that consists of over 150 species, among these, M. alba is dominant[41]. Biochemical compounds such as Moranolin (deoxynojirimycin (DNJ)), Moran (glycopeptides), hydrophobic flavonoids (flavones and flavonone), 2 arylbenzofuran, and ethanolic extract, flavonoids, polyphenols, carotenoids, vitamin A, vitamin C, vitamin E, ethyl acetate, γ -aminobutyric acid, flavanics are isolated from different parts of mulberry plants which have anti-obesity, lipid-lowering effects[42]. They also suggested that ethanolic extract obtained from mulberry leaves showed anti-obesity action on diet-induced mice [43].

11) ***Cinnamomum zeylanicum:-*** It is produced from the bark of trees from the genus *Cinnamomum. It* belongs to the Lauraceae family. A recent study suggests that cinnamon extract reduces lipid and glycogen accumulation in the livers of high fat diet-fed animal models and lowers glucose levels by increasing insulin secretion[44-45]. Oral administration of CE significantly increased UCP1 expression in the subcutaneous adipose tissue *in vivo* and reduced the body weight of the DIO mice[44].

12) ***Morinda citrifolia (noni) :-*** It is popularly called as noni or Indian Mulberry has apparent beneficial effects on human health. Noni fruit include phenolic compounds, anthraquinones, carbohydrates, organic acids, alcohols, vitamins, flavonoids, iridoids, ketones, lignans, triterpenoids, nucleosides, sterols, fatty acids, carotenoids, and many others[46]. *Momordica charantia* (MCE) and *Centella asiatica* (CAE) extracts in lipoprotein lipase (LPL) inhibition and the effects of the extracts in proliferation and differentiation of 3T3-L1 preadipocytes[47].

13) ***Alisma orientalis:-*** It is a well-known traditional Chinese medicine Zexie to treat various illnesses in China, such as obesity, diuretic, diabetes, hyperlipidemia, and detumescence. incuding two guaiane-type sesquiterpenoids, one eudesmane-type sesquiterpenoid, and two protostane-type triterpenoids. It inhibits the pancreatic lipase enzyme, important for anti-obesity action[48].

14) ***Scutellaria baicalensis :-*** It is also known as common skullcap, contains Baicalin as

phytochemical. Inhibition of adipogenesis in 3T3-L1 preadipocytes, and prevention of dyslipidemia to decrease epididymal fat, hyperlipidemia, liver steatosis and body weights in murinae fed with high fat diet[49]. Treatment of 3T3-L1 preadipocytes with baicalin inhibited triglyceride accumulation and lipid droplet formation during adipogenesis [50].

15) ***Enicostemma littorale :-*** The aerial part of the E. littorale reduces the serum cholesterol level in hepatoma bearing rats which induces hypercholesterolaemia. A component of plant enhances cholesterol acyltransferase by esterification of free cholesterol. Hypolipidemic and antioxidant effects were evaluated by administrating an aqueous extract of E. littorale to rats (1.5 g/100 g body weight/day) along with hypercholesterolaemic diet for 6 weeks. The treatment with this extract decreases the activities of erythrocyte CAT, SOD and LPO levels, with an increase in reduced glutathione levels, liver and kidney cholesterol levels were also decreased in E. littorale treated rats when compared to cholesterol fed untreated rats [51].

16) ***Gelidium amansii: -*** *Gelidium amansii*, a well-known red alga, has been consumed since ancient times. GAE supplementation significantly decreased body weight gain, adipose tissue mass, leptin concentration, and the levels of TG and TC in the plasma and liver. Furthermore, GAE was also shown to decrease the expression levels of the adipogenic transcription factors SREBP-1c, FAS, PPARγ, and C/EBPα, and increase pAMPK expression[52].

17) ***Adiantum capillus veneris :-*** It contains alkaloids, flavonoides, tannins, saponins, terpenoids, steroids, glycosides, and reducing sugars aldehyde, amides, alcohol, carboxylic acid, ketone, and ethers[53]. *A. capillus-veneris* exerted significant antiobesity ($p < 0.001$) with marked triacylglycerol-reducing capacities ($p < 0.001$) in comparison to rats fed with HCD for 10 weeks[54].

18) ***Achyranthes aspera: -*** Achyranthes aspera (Amaranthaceae) is an important medicinal herb found as a weed throughout India. Though almost all of its parts are used in traditional systems of medicines, seeds, roots and shoots are the most important parts which are used medicinally. It contain Saponins, oleonolic acid, dihydroxy ketones, alkaloids, long chain compounds [55].A.aspera was evaluated using cholesterol induced hyperlipidemia in albino wistar rats. Both the extracts of ethanolic and aqueous were shown antihyperlipidemic activity[56].

19) ***Adiantum capillus-veneris :-*** Adiantum is a genus of ca. 200 species in the family Adiantaceae, distributed extensively over the world from cool temperate zones to hot tropical regions. It contains Terpenoids, Flavonoids, Phenyl propanoids, Steroids, Alicyclic acids[57]. Due to the presence of Chlorogenic acid, Ellagic acid, Ferulic acid, it shows the pancreatic lipase inhibition activity[58].

20) ***Citrus unshiu :-*** It is an economically important fruit on Jeju Island, Korea, but byproducts are a major source of agricultural waste[59]. It contains, Hesperidin, neohesperidin, narirutin, and naringin as the main flavonoids in Citrus unshiu, show the porcine pancreas lipase inhibiting activity. In animal experiments, the concentration of plasma triglyceride in rats fed a diet containing 10% hesperidin were significantly lower than that fed the control diet[60].

CONCLUSION:

Patients of obesity are increasing drastically not only in the world but also in india. Amylin, Leptin, GLP-1, and MC4R analogues are generally considered as the recent targets but more studies are required to understand the mechanism. While on other hand current treatment have more side effects. Utilization of Herbal medicine along with conventional drug definitely promotes health or cure diseases in the positive way. Cosmos kunth, edible mulberries, certain algaes are the best examples. Natural Products will open the new era of the treatment of the obesity.

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