HERBAL APPROACH FOR TREATMENT OF OBESITY
– A REVIEW
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Abstract:
Obesity is termed as “New World Syndrom” and considered as major health problem by WHO. It is associated with excessive fat accumulation in the body and measured by BMI [Body mass index]. It is caused by imbalance between food intake and energy expenditure. Various pharmacological treatments are available to affect different targets but the incidence of side effect of these compounds like rhabdomyolysis and others. Therefore herbal path is most effective and give less or no side effects as compared to pharmacological treatment. Datas on 15 recent medicinal plants are reviewed and taking consideration for exact mechanism of action, related phytoconstituent and pharmacological evaluation etc.
In the modern era there is need for developing awareness regarding more use of herbal preparation thereby promoting weight loss and combating obesity.

Key Words: Obesity, Body mass index, rhabdomyolysis, Phytoconstituents, herbal preparation.

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1. INTRODUCTION:

Obesity is disorder which involves excessive body fat. This fat accumulates into the adipose tissues and other organs like liver, skeletal muscles. It is measured by Body mass index (BMI) which is used to differentiate the person as underweight, overweight, normal or obese. BMI is ratio of person’s weight in kilogram to the square of heights in meters. A BMI ≥25 kg/m² is defined the person is overweight and ≥30 kg/m² is obese. Obesity is one of the major risk factor for increasing health problems. It leads to hypercholesteremia, hyperlipidemia, atherosclerosis, hypertension, diabetes mellitus etc.[1]

The obesity can be categorised into two way: 1) excessive intake of foods with high salt, fats and sugars but loss of minerals, vitamins and other nutrients. 2) decreased or no exercises and other physical activity because of more sedentary life style and more use of transportation. Therefore the main etiology behind obesity is an imbalance between energy uptake and expended. Our body needs some energy or calories from foods for basic functions. When calorie consumed and expended are equal then body weight is maintained.

If more calorie taken then burned, the resulting condition moves towards weight gain, over weight and finally obese. Because of highest mortality and morbidity, an obesity requires proper management and treatment[2]. This includes pharmacotherapy, diet plan and exercises. Certain foods that inverts metabolism of fats and lipids should be avoided. Statins like drugs, for example Atorvastatin inhibits HMG Co A reductase enzyme and widely used as allopathic treatment for obesity. Others are bile acid sequestrants, Fibrates, Niacin and Orlistat are the pharmacological treatment for obesity. But the major side effects associated with these drugs are rhabdomyolysis and others are allergic reactions such as wheezing, shortness of breathing, cough, swelling of face, tounge etc.[3] To overcome all these side effects herbal products are safe, having no or less side effects as compared to chemically synthesized compounds. Although herbal drugs are easily available without any prescription and advancement in technology, herbal preparations are still in contact with pharma market due to their wider acceptance, cost effective and faith of people in using herbs that it is 100% natural origin means safe, thereby nowadays herbal products and their demand is going to be increased[4]. Present review focuses on mechanism, Pathophysiology behind the obesity and various herbs used in treatment of obesity.

2. Epidemiology:

Obesity and overweight are the major leading cause of death. Obesity is found in almost all countries in the world. Around 2.8 millions die due to obesity. WHO found that in the year 2016, around 1.9 billions adults, 18 years and above were overweight and of these 650 millions were obese. 41 million children under the age of 5 were overweight or obese in 2016. Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016. Overall one in tenth populations in the world are obese. WHO have noticed that the new number of cases of obesity around the World within next two decades will exceed hundred of millions. Childhood obesity is major risk of obesity, premature death and disabled during adulthood. In addition to the future risk, childhood obesity children have suffering from breathing problem, hypertension and cardiovascular disease[5].

3. Etiology:

Factors responsible for obesity are: 1. Environmental factors: This include increase the amount of food intake especially junk food and reducing physical activity like exercises. All these because of busy schedule and sedentary life style, which ultimately leads to accumulation of fats in the body. 2. Genetic factors: Some genes are responsible for predisposing obesity and if parent gene is obese then chances of getting their child become obese or overweight. 3. Physiological factors: There are some internal mechanism in the body including neurotransmitters that stimulate the appetite and reduces energy expenditure. 4. Diseased condition: Diseases like diabetes, hypothyroidism and heart problems are closely related to obesity. 5: Drug induced obesity: For treatment, some pharmacological active ingredients like antipsychotic drugs for example diazepam, cloniphen causes obesity[6].

4. Pathophysiology:

Fat cells consist of 21-38% of total body weight of normal individual, in case of obese people consumption of more calorie than the expended and appetite can not reduce to compensate the more storage of the fats. Adipose tissue is regulated by signals transmitted to brain. The imbalance between transferring a signal from adipose tissue to brain and response of brain to signals results in obesity. This system of energy stores will determine the food intake and energy expenditure[7]. The another mechanism include Leptin hormone secreted by adipose tissue, can give signals to brain about the amount of fat stores. Leptin is secreted in favour of food deprivation, exercises and cold exposure and is inhibited in obesity stage. Now this leptin goes to the
brain and inhibit the release of NPY [NeuroPeptide Y], which stimulate the appetite, synthesis and storage of fats and reduces the energy expenditure. Adipocyte secretes Interleukin-6[IL-6] and its concentration in blood is increased in obese subjects and association with fat mass and BMI.

Adipopectine is also adipocytes derived insulin sensitizing hormone which is decreased in obesity and increased in weight reduction. Adipose tissue of the obese person also expresses the other proteins like TNF α and β,IL-1,IL-6,inducible nitric oxide synthase [iNOS] and increased in obesity[8].

Hyperlipidemia and Obesity:
Hyperlipidemia and obesity both are interrelating condition. Hyperlipidemia is a condition in which there are elevation of plasma lipids in the blood, commonly LDL. It is also termed as hypercholesterolemia or hypelipoproteinemia[9]. Increasing in lipids like LDL, triglyceride and cholesterol are mainly responsible. Hyperlipidemia can occur either due to over production or impaired removal of lipoproteins and defects in lipoprotein or its receptor. There are three types of lipoproteins – LDL, VLDL and HDL. Almost all the dietary fats are absorbed from the intestinal lumen into the intestinal lymph and packed into chylomicrons. These lipoproteins move into the blood stream where they got hydrolyzed by endothelial lipoprotein lipase which hydrolyzes the triglyceride into glycerol and nonesterified fatty acids. After which the chylomicron remnants are absorbed in the liver and packaged with cholesterol, cholesteryl esters and ApoB100 to form VLDL. Low density lipoproteins in excessive quantities accelerate the deposition of LDL on artery walls and lead to atherosclerosis which is strongly related to ischemic heart disease [IHD] while as the high density lipoproteins prevent the deposition of LDL on artery walls and hence are preventive in nature[10]

1. Exogenous Pathway

2. Endogeneous Pathway

Remnant receptor
Cholesterol
\{ Free fatty acid \}

Chyomicron Remnant
Empty HDL

LIVER
Cholesterol and Triglycerides
VLDL

ADIPOSE TISSUE
VLDL
LDL

PERIPHERAL TISSUE
LDL
LDL-R

Fig: 2 Two pathways by which fats accumulates in the adipose tissue.
5. List of Herbal plants utilized for treatment of Obesity:

<table>
<thead>
<tr>
<th>Botanical name</th>
<th>English name/Common name</th>
<th>Parts used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acacia arabica</td>
<td>Babbula</td>
<td>Gum, bark, leaf, fruit-pods</td>
<td>[11]</td>
</tr>
<tr>
<td>Achyranthus aspera</td>
<td>Apamarga</td>
<td>Root, seed, leaf, whole plant</td>
<td>[12]</td>
</tr>
<tr>
<td>Aconitum heterophyllum</td>
<td>Ativisha</td>
<td>Root, rhizome</td>
<td>[13]</td>
</tr>
<tr>
<td>Acorus calamus</td>
<td>Vacha</td>
<td>Rhizome</td>
<td>[14]</td>
</tr>
<tr>
<td>Adathoda vasica</td>
<td>Vasa</td>
<td>Leaf, root, flower</td>
<td>[15]</td>
</tr>
<tr>
<td>Allium sativum</td>
<td>Garlic</td>
<td>Stem, Fruit</td>
<td>[16]</td>
</tr>
<tr>
<td>Aloe vera</td>
<td></td>
<td>Leaf, root</td>
<td>[17]</td>
</tr>
<tr>
<td>Betula utilis</td>
<td>Burja</td>
<td>Bark, nodes</td>
<td>[18]</td>
</tr>
<tr>
<td>Camelia sinensis</td>
<td>Green Tea</td>
<td>Leaves</td>
<td>[19]</td>
</tr>
<tr>
<td>Catharuths roseus</td>
<td>Barmasi</td>
<td>Whole plant</td>
<td>[20]</td>
</tr>
<tr>
<td>Coriander sativum</td>
<td>Coriander</td>
<td>Fruits</td>
<td>[21]</td>
</tr>
<tr>
<td>Cassia tora</td>
<td>Chakramardha</td>
<td>Seed, leaf, root</td>
<td>[22]</td>
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<tr>
<td>Cedrus deodara</td>
<td>Devadaru</td>
<td>Hearwood oil</td>
<td>[23]</td>
</tr>
<tr>
<td>Embelia ribes</td>
<td>Vidanga</td>
<td>Fruit</td>
<td>[24]</td>
</tr>
<tr>
<td>Emblica officinalis</td>
<td>Malamaki</td>
<td>Fruit</td>
<td>[25]</td>
</tr>
<tr>
<td>Garcinia indica</td>
<td>Vrikshamla</td>
<td>Fruit, root, bark, oil</td>
<td>[26]</td>
</tr>
<tr>
<td>Gymnema sylvestre</td>
<td>Meshashringa</td>
<td>Leaf, root, seed</td>
<td>[27]</td>
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<tr>
<td>Holarrhena antidysentrica</td>
<td>Kutaja</td>
<td>Seed, bark</td>
<td>[28]</td>
</tr>
<tr>
<td>Momordica charantia</td>
<td>Karavellaka</td>
<td>Fruit, whole plant, leaf, root</td>
<td>[29]</td>
</tr>
<tr>
<td>Moringa oleifera</td>
<td>Sigru</td>
<td>Root, bark, seed</td>
<td>[30]</td>
</tr>
<tr>
<td>Picrorhiza kurroa</td>
<td>Katuka</td>
<td>Root</td>
<td>[31]</td>
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<tr>
<td>Piper longum</td>
<td>Pippali</td>
<td>Fruit, root</td>
<td>[32]</td>
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<tr>
<td>Piper nigrum</td>
<td>Maricha</td>
<td>Fruit</td>
<td>[33]</td>
</tr>
<tr>
<td>Plumbago zeylanica</td>
<td>Chitraka</td>
<td>Root, bark</td>
<td>[34]</td>
</tr>
<tr>
<td>Punica granatum</td>
<td>Pomegranate</td>
<td>Fruit rind, leaves</td>
<td>[35]</td>
</tr>
<tr>
<td>Terminalia arjuna</td>
<td>Arjuna</td>
<td>Bark, root, leaf</td>
<td>[36]</td>
</tr>
<tr>
<td>Terminalia bellerica</td>
<td>Bibhitaka</td>
<td>fruit</td>
<td>[37]</td>
</tr>
<tr>
<td>Terminalia chebula</td>
<td>Haritaki</td>
<td>fruit</td>
<td>[38]</td>
</tr>
<tr>
<td>Terminalia tomentosa</td>
<td>Asana</td>
<td>Bark, heartwood</td>
<td>[39]</td>
</tr>
<tr>
<td>Thea sinensis</td>
<td>Oolong tea</td>
<td>Leaf</td>
<td>[40]</td>
</tr>
<tr>
<td>Tinospora cordifolia</td>
<td>Guduchi</td>
<td>Stem, root</td>
<td>[41]</td>
</tr>
<tr>
<td>Trachyspermum ammi</td>
<td>Yavani</td>
<td>Fruit</td>
<td>[42]</td>
</tr>
<tr>
<td>Tribulus terrestris</td>
<td>Gokshura</td>
<td>Fruit, root, whole plant</td>
<td>[43]</td>
</tr>
<tr>
<td>Trigonella foenum graceum</td>
<td>Methika</td>
<td>Seed, leaf, whole plant</td>
<td>[44]</td>
</tr>
<tr>
<td>Valeriana jatamansi</td>
<td>Tagara</td>
<td>Root</td>
<td>[45]</td>
</tr>
<tr>
<td>Zingiber officinale</td>
<td>Shunti</td>
<td>Rhizome</td>
<td>[46]</td>
</tr>
</tbody>
</table>

6. Recent literature and Current Drug targets of obesity:
A large number of herbal medicines and supplements are available in current market for the management of obesity. They all are having not same effects, reason behind this is the target they focuses are unique so all follow different mechanism of action. The basic principle behind antiobesity drugs are maintaining the energy balance in the body, that is equilibrium between energy intake and expenditure[47]. The main approaches follows either effect of these drugs on nervous system or effect of supplement on physiological function. All targets by which antiobesity drugs or supplements acting are described as below:

6.1. Pancreatic lipase enzyme inhibition:
Dietary fats are absorbed in the intestine by action through Lipase enzyme that converts fats in to the free fatty acids and monoglycerides. If pancreatic
lipase enzyme is inhibited then ultimately the formation of fatty acid is blocked which in turn leading to weight loss. This inhibitory activity possesses phytoconstituents which includes saponins, phenolic compounds and flavanoids and caffeine. Pharmacological agent Orlistat works on this target[48].

6.2. Thermogenesis:
Increases thermogenesis by metabolism from generation of ATPs thereby conversion of food energy as heat and it ultimately leads to weight loss. There are three types of adipose tissue: 0White, brown and beige adipose tissue. In thermogenesis, brown adipose tissue plays important role in obesity by dissipating excess energy as heat and thereby controlling energy balance. Various naturally occurring compounds like caffeine, capscaice are used in treatment for obesity[49].

6.3. Lipid Metabolism:
The pharmacological target for lipolysis can be envisaged by stimulating triglycride hydrolysis in order to lower down to the fat stores. This will require oxidation of newly released fatty acid, some examples are the flavanoids of leaves of the plant Nelumbo mucifera actve the B-adrenergic receptor and though this pathway it leads to supress the body weight gain. The another example is caffeine, a major phytoconstituent found in oolong tea acts by binding with the phospholipid phosphate group and interaction between the lipase and triglycride portion of lipid droplets and thereby enhances lipolysis[50].

6.4. Centrally acting mechanism: Body weight can be maintained by intake of foods. Many drugs act directly on their effect on the receptor within the central nervous system. The status of body stores and adiposity is regulated by three main hormones leptin, insulin and gastrointestinal peptide such as ghrelin and they all communicate to the central nervous system. For example green tea extract has reported to regulate the plasma leptin concentration. A number of natural appetite suppressants herbs reduce the expression of hypothalamic neuropeptide Y or serum leptin levels. The another mechanism is to alter the various hypothalamic neuropeptide’s CNS level and key CNS appetite neurotransmitter’s level via peripheral satiety peptide system and thereby suppress the appetite[51]. The phytoconstituents found in green tea like catechin- epicatechin. epigallocatechin stimulate thermogenesis by inhibition of catechol- O-methyltransferase enzyme that is responsible for degradation of norepinephrine. The naturally occurring Hydroxy citric acid obtained from Garcenia cambogia is a potential appetite suppressant. It inhibits adenosine 5- triphosphate-citrate lyase which stops acetyl co enzyme A production and decreases fatty acid synthesis.

7. Screening method for antiobesity agents:
The invivo methods and invivo animal models are available for screening of antiobesity drugs.

7.1 Invitro methods:
7.1.1. Pancreatic Lipase Inhibition Assay[52]: Porcine pancreatic lipase [PPL, type II] activity was measured using p-nitrophenyl butyrate [p-NPB] as a substrate. The method used for measuring the pancreatic lipase activity was modified. PPL stock solutions [1 mg/mL] were prepared in a 0.1 mM potassium phosphate buffer [pH 6.0] and the solutions were stored at −20 °C. To determine the lipase inhibitory activity, the extracts [final concentrations 100, 50, 25, 10, 5, 2.5, 1.25 μg/mL] or Orlistat [at same concentrations] as a positive control were pre-incubated with PPL for 1 h in a potassium phosphate buffer [0.1 mM, pH 7.2, 0.1% Tween 80] at 30 °C before assaying the PPL activity. The reaction was then started by adding 0.1 μL NPB as a substrate, all in a final volume of 100 μL. After incubation at 30 °C for 5 min, the amount of p-nitrophenol released in the reaction was measured at 405 nm using a UV-Visible spectrophotometer. The activity of the negative control was also examined with and without an inhibitor. The inhibitory activity [I] was calculated according to the following formula: Inhibitory activity [I%]=100−[(B−b)/(A−a)×100]

7.2. Invivo Animal models[53]:
There are various animal models used for screening of antiobesity drugs.
1. Diet-induced [hypercaloric diets] obesity
2. Chemical agents induced obesity
3. Drug induced obesity
4. Genetic models
5. Monogenic
6. Polygenic models
7. surgical model.
In general, Diet induced and genetic models are more useful for screening of antiobesity effect.

8. Recent herbs used in obesity :
8.1 Achyranthus aspera [Amaranthaceae]:
This plant is having saponins, examples are triterpenoid saponin – Oleanolic acid and others are Pentatriaontane, 6-pentatriacontanone, Hexatriacontane and Tritriacontane. The ethanolic extract of plant shows significant reduction of body
weight and triglyceride and cholesterol level in mice fed a high fat diet for 6 weeks. The mechanism behind this is inhibition of pancreatic lipase enzyme[54].

8.2 Nelumbo nucifera [Nelumboaceae]:
Several bio active phytoconstituents derived from seed, flowers, leaves and rhizomes are belonging to different chemical groups like alkaloids, flavanoids, glycosides, and terpenoids. N.nucifera alkaloids such as roemerine, nuciferin, nelumboside, anonaine shows to inhibit 3T3-L1 preadipocyte differentiation and improve high fat diet induced obesity and body fat accumulation in rats. The flavanoids also inhibit the pancreatic lipase enzyme[55].

8.3 Salacia reticulata [Celastraceae]:
S. reticulata leaves and root bark extracts in the management of patients with prediabetes and mild to moderate hyperlipidemia. Active ingredients of Salacia include salacinol, kotalanol, kotalagenin-16 acetate, and mangiferin. The active ingredients have a variety of actions, including postprandial glucose decrease by inhibiting α-glucosidases in the intestinal brush border, and thus slowing carbohydrate breakdown into absorbable monosaccharides. It contains kotalanol, an α-glucosidase inhibitor, which has an action similar to that of acarbose[56].

8.4 Taraxacum officinale [Asteraceae]:
It is known as dandelion, which belongs to Asteraceae or Compositae family. As a food, dandelion is used as a salad ingredient, in deserts. Leaves are a rich source of a variety of vitamins and minerals. Chemical constituents present in the leaves are bitter sesquiterpene lactones principally also known as bitter principles, several polyphenols and coumarins. Other related compounds include β-amyrin, taraxasterol and taraxerol as well as free sterols [sitosterin, stigmasterin, phytosterin]. The inhibitory activity of dandelion on the pancreatic lipase enzyme has been demonstrated in vitro and in vivo indicating the potential of dandelion as an anti-obesity agent with limited side effects[57].

8.5 Camelia sinensis :
The leaf of camellia sinensis is source of tea and consumed for thousands of year. It contains polyphenol flavanoids epigallocatechin gallate which has lipid lowering properties. Green tea consumption reduces obesity through lowering leptin levels and its effect on hypothalamus[19].

8.6 Mellissa officinalis:
This plant is commonly used as antistress herb. An active fraction denominated ALS-L1023 [ALS] extracted from Melissa leaves by organic solvents exhibited antiangiogenic and studies suggested that the effect of ALS on angiogenesis and ALS can regulate adipose tissue growth in high fat diet-induced obese mice. When high fat diet-induced obese mice were treated with ALS for 8 weeks, adipose tissue mass and adipocyte size were significantly reduced in treated mice compared to control mice[58].

8.7 Bambusa textilis [Bambusoideae]:
Bamboo leaves are potential source of functional foods and are worthy of future development because of their abundance as a natural source with various biological activity. Different phytochemicals, including flavanoids, phenolic acids, phenols and sterols, were found in this bamboo species. Study shows that methanolic extract of Bambusa textilis reduces lipid levels in high fat diet induced rats[59].

8.8 Medicago sativa [Fabaceae]:
Medicago sativa is commonly known as Alfalfa. Alfalfa is mostly seen as a food for grazing animals. Its related to clove and fenugreek. Study suggested that petroleum ether extract of roots of Medicago sativa shows antihyperlipidemic effect. The administration of extract for 4 weeks decreases triglycerides, total cholesterols, LDL, VLDL in comparison to rouvastatin[60].

8.9 Ephedra sinica [Gnetaceae]:
Ephedra has been used as a supplement for weight loss and its effects have been reported. studies found that the influence of Ephedra on the composition of gut microbiota, and its correlation with weight loss. Body weight, body mass index and body fat percentage of subjects were reduced after the consumption of the stem extract of the plant[61].

8.10 Carum carvi [Umbelliferae]:
Caraway [carum carvi] is wellknown plant that is traditionally utilized to treat obesity. It contains multiple phytoconstituents like fatty acid, polyphenols and volatile oils. Weight and fat lowering effect of caraway extract is due to carvacrol [polyphenol] and unsaturated fatty acids[62].

8.11 Morus bombycis [Moraceae]:
Morus bombycis root extract shows strong anti-lipase activity. The extract shows increased lipolytic effect by decreasing intracellular triglyceride and release of glycerol. It also inhibit phosphodiesterase activity that’s why study suggested the plant has an antiobesity effect[63].
8.12 Moringa oleifera [Moringaceae]:
This plant commonly known as Drumstick tree that possesses medicinal values attributed to its whole plant parts such as leaves, root, bark, fruits, and seeds. It contains alkaloids, tannins, terpenoids, flavonoids and steroids. The high concentration of various vitamins and minerals makes it virtually ideal dietary supplements. The hypolipidemic activities of Moringa leaves are associated with β-sitosterol. Study suggested that the methanolic extract of Moringa leaves decreases triglyceride and total cholesterol level in High Fat Diet induced Obesity in rats[30].

8.13 Coleus forskohlii [Lamiaceae]:
Coleus forskohlii is an traditional ayurvedic indian plant used as slimming aids. It belongs to mint family and rich in alkaloids such as forskolin which acts as adenylyl cyclase activator. It stimulate the production of cAMP that triggers metabolic processes, thermogenesis, and stimulate the loss of body fat. Clinical studies on over weight obesity showed that the extract of Coleus forskohlii acts as antiobesity agent was well tolerated and having no adverse effects[64].

8.14 Garcenia indica [Cluciaceae]:
Garcenia is plant of Cluciaceae family, commonly used as flavouring agent. A number of phytochemicals including flavanoids and organic acids are found in plant. Among them Hydroxy Citric Acid is a potential supplement for weight management and as antiobesity agent. The antiobesity effect of HCA is due to serotonin regulation and food intake suppression, decreased lipogenesis, increased fat oxidation and downregulation of spectrum of obesity associated genes[65].

8.15 Syzygium cumini [Myrtaceae]:
It is known as Jamun fruits. Study investigated that ethanolic crude extract of Syzygium cumini was screened for hypoglycemic and hypolipidemic effect. It reduces triglyceride and cholesterol level in alloxan induced diabetic rats. The exact mechanism is not known but it normalizes plasma lipids[66].

CONCLUSION:
Dietary fat is absorbed by action of pancreatic lipase enzyme into the intestine. Therefore the most important target of newer antiobesity agent is pancreatic lipase inhibition and by which the potential of herbs and their effects are to be determined. Various bioactive phytocompounds derived from above mentioned herbs are belonging to different chemical class like alkaloids, glycosides, phenolics and flavanoids that are safe to treat obesity due to harmful side effects from synthetically derived compounds. Herbal products using weight loss plants are marketed nowadays, but so far no systematic screening is attempted to come up with the effect of them. Clinical trials of herbal products are to be must to potentiate their effects and therefore to generate the attraction of herbal products among the users.

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