RESEARCH PAPER

# Pharmacological Screening Model and Phytoconstituent for Anti-Obesity Activity: Comprehensive Overview

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*ABSTRACT*

Obesity is a chronic, multifactorial metabolic disorder characterized by excessive adipose tissue accumulation and dysregulated energy homeostasis. Despite the availability of approved pharmacotherapies and bariatric interventions, their use is often limited by adverse effects, variable efficacy, and restricted accessibility. Consequently, plant-derived phytoconstituents have gained increasing attention as complementary or alternative therapeutic candidates for obesity management. Numerous phytochemicals - including polyphenols, flavonoids, alkaloids, terpenoids, glycosides, and saponins - exert anti-obesity effects by modulating multiple metabolic pathways such as lipid absorption, adipogenesis, thermogenesis, appetite regulation, and insulin sensitivity. However, systematic pharmacological screening is essential to validate their mechanistic actions and therapeutic relevance. This review summarizes key phytoconstituents with documented anti-obesity potential and highlights their underlying mechanisms, including inhibition of pancreatic lipase, activation of AMP-activated protein kinase (AMPK), suppression of adipocyte differentiation, enhancement of lipid oxidation, and modulation of gut microbiota. In addition, the review outlines major in vitro and in vivo screening models used in anti-obesity research. In vitro assays, such as pancreatic lipase inhibition, adipocyte differentiation in 3T3-L1 cells, and AMPK activation studies, provide mechanistic insights at the molecular level. In vivo models - including high-fat diet-induced obesity, genetically modified models, and chemical induction models - offer comprehensive evaluation of physiological, metabolic, and behavioral outcomes. Overall, the review emphasizes the importance of integrating phytochemical exploration with robust pharmacological screening models to advance the development of effective, safe, and evidence-based plant-derived anti-obesity therapeutics.

**Keywords:** Obesity, Phytoconstituents, Screening models, 3T3-L1, Pancreatic lipase, Diet induced obesity, Flavonoids, AMPK, Adipogenesis, Zebrafish.

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## 1. INTRODUCTION

An unhealthy or excessive buildup of body fat is called obesity. An energy imbalance occurs when caloric intake continuously surpasses energy expenditure due to a sedentary lifestyle and excessive consumption of simple carbs and fats. Over time, obesity develops as a result of the body storing extra fat due to this imbalance. This imbalance causes extra energy to be stored as triacylglycerols (TGs), mostly in the abdominal region. This growth and increase of fat cells (adipocytes) in white adipose tissue ultimately contribute to the development of obesity [1]. A body mass index (BMI) of more than 25 kg/m2 indicates that someone is overweight, while more than 30 kg/m2 is considered obese. The World Health Organization (WHO) reports that since 1975, the number of obese people worldwide has almost tripled, and that being overweight or obese causes at least 2.8 million deaths annually [2]. Furthermore, obesity has grown exponentially in India in the twenty-first century, posing a serious threat to people's health and productivity. A different study on the nutritional health of rural Indians predicts that 20% of rural Indian adults will be overweight or obese by 2030 [3]. Overweight and obesity significantly increase the burden of chronic illnesses and their impact worldwide [4]. As a pathological state, it is frequently associated with a higher probability of a number of diseases, including type 2 diabetes, dyslipidemia, hypertension, fatty liver disease, osteoarthritis, sleeplessness, cardiovascular diseases, gallstones, and cancer [5]. Constipation, nausea,

insomnia, gastrointestinal problems, and potentially dangerous cardiovascular consequences are among the side effects of some drugs used to treat clinical obesity [6]. Therefore, research is being done to discover and develop anti-obesity diets and food ingredients that would effectively reduce body fat accumulation, lower the risk of obesity-related chronic diseases, and limit side effects during clinical therapy [6].

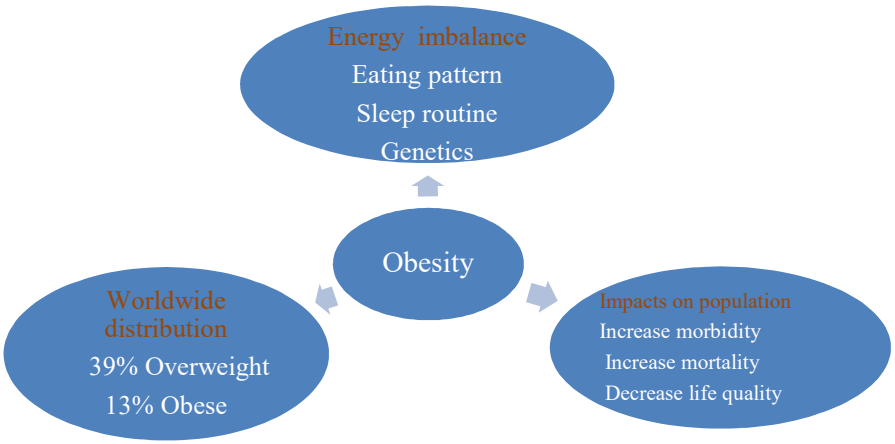
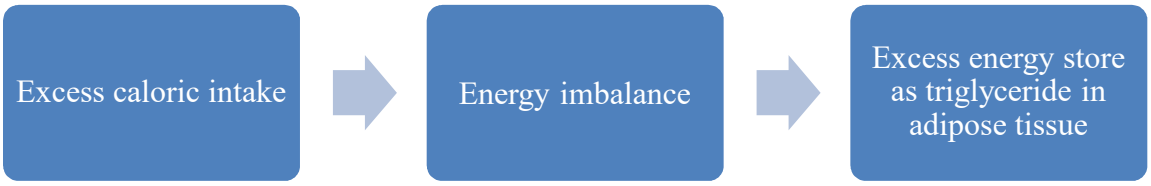


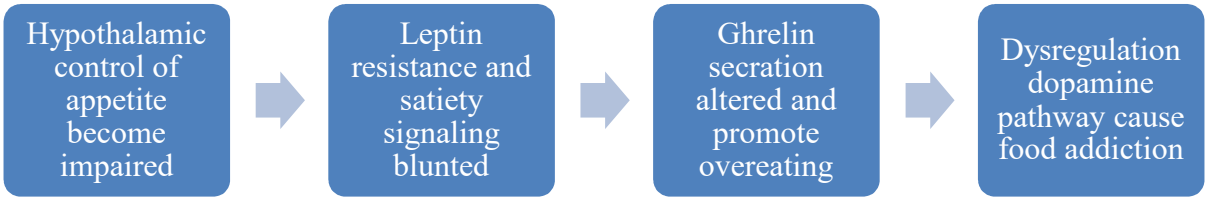

**Fig 1 -** Overview of obesity

**1.1 Pathophysiology**

1.1.1 Energy imbalance




1.1.2 Neurohormonal dysregulation




1.1.3 Insulin resistance

**Fig 2** - Pathophysiology of obesity based on Energy imbalance, Neurohormonal dysregulation, Insulin resistance [7].

## 2. PHARMACOLOGICAL SCREENING MODELS

### 2.1 In Vitro Models

2.1.1 Enzyme assay

Pancreatic Lipase Inhibitory Assays-

P-nitrophenyl esters are commonly used as substrates in the pancreatic lipase inhibition assay; however, long-chain esters frequently cause turbidity because they release insoluble fatty acids. Unlike Triton X-100 or gum Arabic, sodium deoxycholate (SDC) prevents turbidity without inhibiting enzyme function, making it the preferable emulsifier to avoid this problem. $CaCl_2$ can also lower turbidity, however it is less practical because it needs an extra removal step. The assay conditions described in the literature vary greatly, but they typically include incubation durations of 5 to 30 minutes and temperatures between 25 and 37 °C. In contrast to 25 °C, which offers superior enzyme stability, particularly for longer experiments, lipase rapidly loses activity at 37 °C - roughly 50% within 5 minutes. Additionally, high temperatures promote the hydrolysis of non-enzymatic substrates, which can affect the outcome. Pancreatic lipase is most active at pH 8.0 in phosphate buffer, with an ideal pH range of 7.0-8.5. Readings obtained at 348 nm (the isosbestic point) are more reliable since pH variations can affect absorbance measurements at 405-410 nm. At concentrations up to 10%, a number of co-solvents, including ethanol, methanol, isopropanol, DMSO, and acetonitrile, are well tolerated; ethanol can be used up to 20% and methanol or DMSO up to 30% without significantly altering enzyme activity. Although lipase solutions should ideally be made fresh, the enzyme can be kept in 10% glycerol at -20 °C for up to three weeks without losing its activity. A maximum final concentration of ≤10% in the assay mix is advised for substrate stock solutions, which are typically made in acetonitrile [8].

2.1.2 Adipocyte differentiation assay-

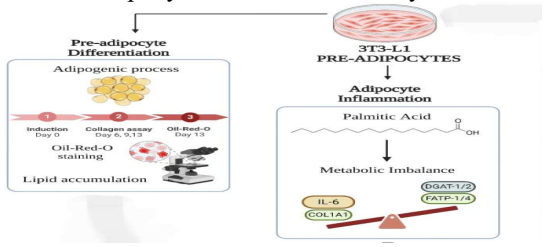



**Fig 3-** Adipocyte differentiation assay

3T3-L1 MBX (ATCC CRL-3242) were kept in GlutaMAX - supplemented DMEM high glucose with 10% FBS and 1% penicillin-streptomycin. Cells were stimulated to differentiate with IBMX, insulin, dexamethasone, and rosiglitazone once they reached approximately 80% confluency. Lipid buildup measured by Oil Red O staining was used to optimize the doses of insulin and dexamethasone as well as the length of the induction. A 5 mM stock of dexamethasone was made in ethanol and kept at -80 °C; a 1 mM intermediate stock was made in DMEM and kept at -20 °C. For differentiation, a final effective concentration of 10 µg/mL of insulin was diluted from a stock of 10 mg/Ml [9]

2.1.3 3D Chip model

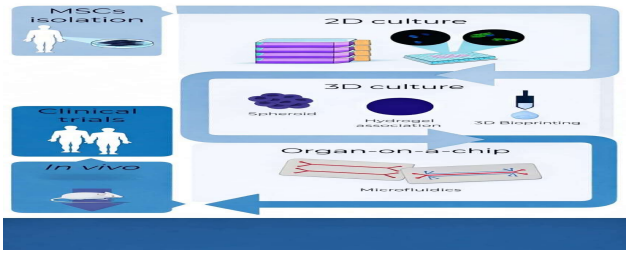



**Fig 4** - 3D Chip model

While epididymal fat from diet-induced obesity C57BL/6J mice (17–20 weeks old) was obtained right after CO2 euthanasia, human peri-colonic adipose samples were acquired under IRB-approved protocols, kept in RPMI, and processed without identification. To prepare the tissue, 100 mg of adipose samples were cut to remove large blood arteries, chopped into pieces around 1 $mm^3$ in size, cleaned, and then placed to either 48-well plates or flow chambers. Several tests were used to evaluate tissue viability and functional activity. Effluent was collected every 24 hours for the Alamar Blue assay, and absorbance between 570 and 600 nm was used to calculate the reduction %. TX-100 was used as a positive control for induced cell death in the LDH experiment, which examined the cytotoxicity of effluent kept at -80°C.

**2.2 In Vivo Model**

2.2.1 High fat diet induced model

2.2.1.1 Rat model

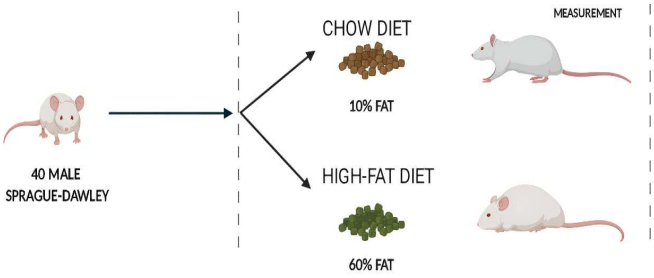



**Fig 5 -** High fat diet induced rat model.

Male rats were shipped at 14 weeks of age after being reared on either standard chow or a high-fat/high-sucrose diet from weaning. Their body weight, weekly food intake, and body composition (fat mass by NMR) were tracked during the study after two weeks of acclimation under controlled light-dark circumstances. At 21 weeks, an oral glucose tolerance test was conducted using a 1.5 g/kg oral glucose dosage after an overnight fast. Blood was drawn for insulin and glucose at various intervals. Rats were slaughtered for tissue collection, including epididymal fat, after additional fasting and fed blood samples were taken at 25–26 weeks. Adipose tissue total RNA was separated, A glycerol test was used to measure the amount of lipolytic activity in the collected effluent, and either insulin or isoproterenol was added as a stimulant through the input media. Flow chambers were quickly opened at the conclusion of each experiment, and tissues were either frozen for RNA extraction or ready for imaging. Tissues were fixed in PFA, stained with PLIN1, CD45, and DAPI, mounted, and examined under a ZEISS LSM900 confocal microscope for confocal imaging. The Qiagen lipid kit was used to isolate RNA, which was then transformed into cDNA and submitted to RT-qPCR analysis using SYBR Green. The $2^{-\Delta\Delta Ct}$ quantification method was used to process the gene expression data, and two-way ANOVA and paired t-tests with Tukey correction were used for statistical comparisons [10,11,12].

2.2.1.2 Zebrafish Model

hybridized to Affymetrix RAE230_2 microarrays, and data quality was rigorously screened prior to analysis. MAS5-processed data with criterion of $P < 0.05$, fold change > 1.2, and absolute signal change > 250 were used to identify differential gene expression. Gene-expression patterns were interpreted using GSEA, hierarchical clustering, classification analyses, and Gene Ontology enrichment. TaqMan real-time PCR was used to validate the chosen genes, normalizing to ARBP. All experiments were conducted in triplicate. Every animal procedure adhered to institutional and NIH-approved protocols [13,14,15,16,17].

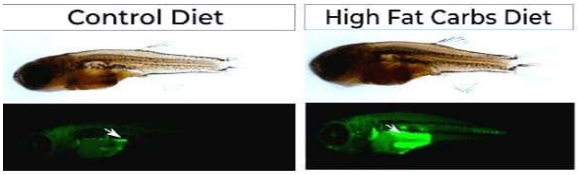



**Fig 6-** High fat diet induced zebrafish model.

In comparison with rat models, where food modification starts just after weaning, zebrafish obesity is typically caused by high fat intake, with overfeeding starting as early as 5 days after fertilization. Lipid accumulation and whole-larval triacylglycerol levels are useful indicators of the evolution of obesity, despite the absence of white adipose tissue in early larvae. Adiposity in larvae and juveniles is quickly increased by high-fat diets, particularly chicken egg yolk solutions. Overfeeding Artemia, which resulted in elevated BMI, hypertriglyceridemia, and fatty liver-metabolic alterations resembling those seen in mammals was the first example of diet-induced obesity in people. Obesity is also caused by other techniques, such as high-fat tailored diets using vegetable, lard, or maize oil. It's interesting to note that whereas high-fat diets result in metabolically unhealthy obesity with glucose intolerance, hepatic steatosis, and increased visceral fat, overfeeding normal-fat meals causes metabolically healthy obesity. This reflects the "obesity paradox" in humans, showing that visceral fat, as opposed to total body weight, is a more reliable indicator of insulin resistance and the risk of diabetes, indicating conserved fat-distribution effects across species [18,19].

2.2.2 Genetic Models of Obesity-

The high retention of metabolic pathways across fish and mammals makes zebrafish useful models for hereditary obesity. Obesity-related phenotypes, such as increased adiposity, hyperlipidemia, fatty liver, and glucose intolerance, are induced by transgenic methods, such as over expressing the melanocortin antagonist AgRP, depleting lipid-regulating miR-27b, or ectopically expressing active AKT1. These methods show conserved central and peripheral metabolic regulation. Key genes related to lipid metabolism, the development of adipose tissue, and hepatic steatosis are also revealed by a number of mutant zebrafish lines. Fatty liver or altered adiposity are caused by mutations that impair ER stress pathways, vesicular transport, ketone body export, pancreatic function, vitamin D metabolism, growth hormone signalling, and fat-distribution processes. The distribution of adipose tissue is conserved in models like gh1, cyp2r1, and plxnd1 mutants, and the risk of metabolic disease is more strongly associated with visceral fat. These transgenic and mutant zebrafish models work well together to advance therapeutic studies and analyze the mechanisms underlying obesity and lipid control [18].

2.2.3 Chemical induced obesity model-

NMRI and C57BL/6 mice were fed normal chow (3.4 kcal/g) and housed at 23 °C with a 12-hour light/dark cycle. From postnatal days 2 through 8, newborn mice were given subcutaneous injections of monosodium glutamate (MSG) at a dose of 4 mg/g body weight. One popular chemical obesity model is monosodium glutamate (MSG)-induced obesity, especially in mice. According to research, giving MSG to newborns damages the hypothalamus, particularly the arcuate nucleus, which affects energy balance and appetite control and eventually results in adult obesity. Numerous studies show that animals treated with MSG had hyperinsulinemia, increased adiposity, and metabolic abnormalities similar to those associated with human obesity. For instance, a 2022 study confirmed the validity of MSG as a metabolic dysfunction model by showing that rats given neonatal MSG experienced notable increases in body weight, fat mass, and insulin resistance. Another open-access study assessed how MSG affected inflammatory markers in a mouse model of obesity caused by MSG. The researchers discovered that prolonged exposure to MSG caused significant weight gain, oxidative stress, and increased pro-inflammatory cytokines. The usefulness of MSG as a non-genetic, inexpensive, and repeatable paradigm for obesity research is further supported by these results [20,21].

## 3. ACTIVE PHYTOCONSTITUENTS AND ITS MECHANISMS

**Table 1-** Active phytoconstituents and mechanisms

| Phytoconstituents | Mechanisms | References |
|---|---|---|
| Curcumin | Anti-inflammatory, enhances lipid metabolism, modifies adipocyte differentiation, and has beneficial effects on the microbes in the gut. Curcumin reduces oxidative stress, inflammation, and insulin resistance, among other metabolic diseases linked to obesity | 22 |
| Quercetin | Boosting heat generation, preventing the synthesis of fat, controlling the metabolism of fat, lowering inflammation, enhancing insulin sensitivity, | 23,44 |

| | | |
|---|---|---|
| | controlling the digestive system, and preventing adipogenesis | |
| Ellagic acid | Reducing Rb phosphorylation, preventing the G1/S phase transition, preventing 3 T3-L1 terminal differentiation of fat cells, and preventing lipid accumulation could all be ways to reduce the concentration of 3 T3-L1 | 23 |
| Epigallocatechin-3-gallate (EGCG). | The modulation of the STAT1/SLC7A11 pathway, gut microbiota, leptin, and other mechanisms have steadily gained recognition in the treatment of obesity | 24 |
| Capsaicinoids | TRPV1 activation leads to decreased appetite, enhanced thermogenesis, and energy expenditure | 25,26 |
| Isoflavones | Control PPAR signalling, adipocyte development, and the estrogenic effects in adipose tissue | 25 |
| Allicin | Raises the body's metabolic rate by triggering the adrenal gland to generate adrenaline, which speeds up the body's fat metabolism and aids in calorie burning and weight loss | 27 |
| Hydroxycitric acid | Reduced food intake and increased fullness can result from HCA's increased central serotonin availability or signalling | 28 |
| Berberine | Turns on AMPK Inhibits adipocyte differentiation, increases insulin sensitivity, and decreases lipogenesis | 29,30 |
| Capsaicin | Reduce oxidative stress, increase fatty acid oxidation, and increase energy expenditure | 31 |
| Chlorogenic acid | Preadipocyte population growth was suppressed by chlorogenic acid, which may offer a suggested method for lowering obesity | 32 |
| Ursolic acid | Ursolic acid boosted brown fat, a tissue that shares skeletal muscle's embryonic origins. Ursolic acid reduced obesity, enhanced glucose tolerance, and lowered hepatic steatosis by increasing energy expenditure in line with increased skeletal muscle and brown fat. These findings point to ursolic acid as a possible treatment for obesity and obesity-related diseases and support a model in which it decreases obesity, glucose intolerance, and fatty liver disease by boosting skeletal muscle and brown fat | 33,34 |
| Saponins | Saponins suppress appetite mainly by modulating gut-brain hormonal and neurotransmitter pathways. They downregulate hypothalamic orexigenic signals (especially neuropeptide Y, NPY), improve leptin signaling and leptin sensitivity by increasing hypothalamic leptin receptor expression, and reduce circulating leptin levels through decreased adipose tissue mass. Additionally, saponins enhance satiety hormones such as cholecystokinin (CCK) and stimulate inhibitory neurotransmitters like serotonin (5-HT) from the gut, collectively leading to reduced food intake, energy consumption, and body weight. | 35,36,37,38, 39,40 |
| Gallic acid | It has been demonstrated that gallic acid preferentially targets adipose tissue to reduce lipogenesis, enhance insulin signalling, and simultaneously counteract elevated oxidative stress and pro-inflammatory response | 41,42,43 |
| Flavonoid | Fruits and vegetables high in flavonoids are thought to prevent weight gain by increasing feelings of fullness | 44 |
| Resveratrol | Apoptosis stimulation, increased lipolysis, inhibition of adipogenesis, and modification of the expression of lipogenesis-related genes | 44 |
| Pregnane | Reduce ORX peptide, NPY level, and hunger | 44 |
| Conjugated linoleic acid | Energy expenditure and lipolysis | 44 |
| Alpha-linolenic acid | Increased lipogenesis and hepatic lipolysis | 44 |
| Docosapentaenoic acid | Increased lipogenesis and hepatic lipolysis | 44 |
| Eicosatetraenoic acid | Increased lipogenesis and hepatic lipolysis | 44 |
| Glucomannan | Delaying the emptying of the stomach, adipogenesis | 44 |
| Cinnamaldehyde | Reduced levels of leptin, free fatty acids, and blood lipids; decreased body weight, fat mass, and food intake; improved insulin sensitivity in obese mice induced by a high-fat diet; prevented adipocyte hypertrophy (fat cell | 45,46,47 |

| | | |
|---|---|---|
| | enlargement); caused browning of white adipose tissue; oral administration increased UCP1 expression in white adipose tissue; and upregulated thermogenic and adipogenic regulators (PGC-1α, PRDM16, and PPARγ) in both brown and white adipose tissues. | |

## 4. CONCLUSION

Phytoconstituents work through a variety of complimentary pathways that collectively target the multifactorial character of obesity, making them a promising and versatile source of anti-obesity medications. By promoting thermogenesis, controlling appetite and lipid metabolism, altering the composition of the gut microbiota, inhibiting pancreatic lipase activity to decrease fat absorption, and suppressing adipogenesis and lipid accumulation in adipose tissue, these bioactive plant compounds have been demonstrated to improve energy expenditure. Using trustworthy and methodical pharmacological screening platforms is crucial to successfully identifying, validating, and converting these phytoconstituents into promising medicinal candidates. Starting with high-throughput in vitro experiments to quickly screen drugs for effects on adipocyte differentiation, lipid metabolism, inflammation, and energy balance, a logical and integrated research pipeline should be implemented. In order to examine efficacy, mechanism of action, and safety in a physiologically realistic setting, promising candidates from these assays should next be assessed in vivo using well-established obesity models, including genetic models (such as ob/ob or db/db mice) and diet-induced obesity models. A tiered approach like this increases the translational significance of preclinical data while simultaneously increasing screening efficiency. However, despite promising experimental results, a number of obstacles still prevent plant-derived anti-obesity medications from being used in clinical settings. It is necessary to use sophisticated formulation techniques and strict quality control to comprehensively address problems with poor bioavailability, variability in phytochemical composition, lack of standardization, and inconsistent dosing. Furthermore, well-planned and sufficiently powered clinical trials are essential for confirming safety and efficacy in humans. To fully realize the therapeutic potential of phytoconstituents as efficient, secure, and long-lasting anti-obesity medications, it will be essential to address these issues through interdisciplinary research.

**List of Abbreviations**

| | |
|---|---|
| AMPK | AMP-activated protein kinase |
| TG | Triacylglycerol |
| BMI | Body mass index |
| WHO | World Health Organization |
| SDC | Sodium deoxycholate |
| DMSO | Dimethyl Sulfoxide |
| DMEM | Dulbecco's modified eagle medium |
| FBS | Fetal Bovine Serum |
| IBMX | 3-isobutyl-1-methylxanthine |
| RPMI | Roswell Park Memorial Institute |
| RT-qPCR | Reverse Transcriptionquantitative Polymerase Chain Reaction |
| NMR | Nuclear Magnetic Resonance |
| GSEA | Gene Set Enrichment Analysis |
| MSG | Monosodium glutamate |
| LDH | Lactate Dehydrogenase |
| ANOVA | Analysis of Variance |

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