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BERBERINE IN OBESITY THERAPY: FROM MOLECULAR MECHANISMS TO CLINICAL APPLICATIONS

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Abstract

Objective:

The study aimed to explore the therapeutic potential of berberine in obesity treatment, with a particular focus on its effects on key metabolic mechanisms, inflammatory processes, and gut microbiota composition.

Materials and Methods:

This review encompasses an analysis of preclinical and clinical studies examining berberine's mechanisms of action, including AMPK pathway activation, lipid profile regulation, white adipose tissue browning, and gut microbiota modulation. Data on berberine's bioavailability and advanced delivery systems were also included.

Main results:

Studies demonstrate that berberine improves anthropometric parameters (BMI, waist circumference), promotes adipose tissue remodeling, and supports glycemic control. It exhibits anti-inflammatory properties, reduces inflammatory markers, and modulates gut microbiota to enhance metabolic processes. Advanced delivery systems have improved its bioavailability, enhancing clinical efficacy.

Conclusions:

Berberine shows multifaceted potential as a complementary therapy for obesity, especially when combined with lifestyle interventions. It offers a safe and effective alternative for addressing this global health challenge.

Keywords: berberine, obesity, insulin sensitivity, gut microbiota, bioavailability

1. Introduction

Obesity is one of the greatest health challenges of the modern world, considered a global epidemic. According to the World Health Organization (WHO), obesity is defined as excessive accumulation of body fat [1]. It is a chronic, progressive, and recurrent disease that results from many complex factors and leads to numerous adverse health consequences, both metabolic and psychosocial [2]. The main cause of obesity is energy imbalance, resulting from excess calories consumed relative to energy expended. Such a condition can interfere with metabolic signaling, leading to further accumulation of body fat [2]. Obesity is classified, among other things, based on body mass index (BMI), calculated as the weight ratio in kilograms to the square of height in meters (kg/m^2). According to accepted norms in adults, a BMI of 25 to 29.9 indicates overweight; a BMI $\geq$30 defines obesity, which is divided into three grades: moderate (30-34.9), severe (35-39.9), and extreme ($\geq$40) [1]. Other more advanced methods to directly assess body fat or obesity include bioelectrical impedance analysis, computed tomography, and magnetic resonance imaging [3].

Obesity increases the risk of many chronic diseases, including type 2 diabetes, hypertension, atherosclerosis, and other cardiovascular diseases, some cancers, including colon cancer and pancreatic cancer, and musculoskeletal diseases such as osteoarthritis [2, 3]. The condition is also associated with chronic inflammation and endocrine disruption, further exacerbating metabolic problems [4]. Globally, the number of people with obesity is steadily increasing, requiring urgent action in both prevention and treatment.

Berberine (BBR) is a natural benzylisoquinoline alkaloid present in plants such as the common barberry (Berberis *vulgaris*) and Indian barberry (Berberis *aristata*). This substance exhibits broad pharmacological properties, affecting many cellular and molecular processes

[5]. Studies have shown that berberine increases insulin sensitivity, lowers blood glucose levels, reduces the risk of metabolic syndrome, improves lipid metabolism, and stimulates weight loss [6]. Earlier reports highlighted that berberine increases adiponectin mRNA expression, inhibits adipocyte differentiation, regulates glucose and lipid metabolism, and reduces leptin and resistin secretion [7]. Meta-analyses indicate that berberine supplementation may contribute to a reduction in body mass index and waist circumference. However, these effects may depend on the dose and length of therapy [8].

The present study aims to analyze berberine's potential as a supportive agent for obesity therapy, with a particular focus on its effects on key metabolic mechanisms, modulation of inflammatory processes, and regulation of gut microbiota composition.

2. The multifaceted impact of berberine on obesity treatment

2.1. Berberine's effects on lipid accumulation and lipid profiles

2.1.1. Preclinical studies

Extensive preclinical research has demonstrated berberine’s efficacy in reducing lipid accumulation in adipocytes and improving lipid metabolism via multiple mechanisms. Berberine has been shown to downregulate key adipogenic genes, such as PPARγ (peroxisome proliferator-activated receptor gamma), C/EBPα (CCAAT-enhancer-binding proteins), and SREBP-1c (sterol regulatory element-binding protein 1), while simultaneously upregulating genes involved in energy expenditure, such as Atgl (adipose triglyceride lipase) [9]. These actions are mediated through potent activation of the AMP-activated protein kinase (AMPK) pathway, a central regulator of energy homeostasis. By activating AMPK, berberine inhibits anabolic processes like lipogenesis (e.g., through suppression of acetyl-CoA carboxylase). It enhances catabolic processes such as fatty acid beta-oxidation, leading to reduced lipid deposition in adipose tissue, liver, and skeletal muscle [10].

Berberine also inhibits preadipocyte differentiation into mature adipocytes, limiting the formation of new fat cells. Additionally, it promotes thermogenesis in both white and brown adipose tissue by increasing the expression of UCP1 (uncoupling protein 1) through the AMPK/SIRT1 axis, further boosting energy metabolism [11]. For example, in a study using 3T3-L1 adipocytes, berberine significantly inhibited lipid accumulation by regulating adipogenic transcription factors and enhancing fatty acid oxidation via AMPK activation [12].

In vivo, studies on high-fat diet (HFD)-induced obese animal models demonstrated that berberine ameliorates dyslipidemia and reduces ectopic lipid deposition. It achieves this by modulating mitochondrial biogenesis and fatty acid oxidation [13]. These results are corroborated by research confirming that berberine stimulates thermogenesis and energy expenditure, making it a promising candidate for anti-obesity therapies [14].

2.1.2. Clinical Studies

Clinical investigations have confirmed the lipid-lowering and metabolic benefits of berberine in humans, consistent with preclinical findings. For instance, berberine supplementation at doses of 500 mg/day has been shown to reduce triglycerides, LDL cholesterol, and total cholesterol while increasing HDL cholesterol levels [15]. These lipid-modulating effects are

thought to result from berberine's ability to regulate cholesterol absorption, bile acid metabolism, and adipokine secretion, as well as its interaction with gut microbiota [15, 16].

In women with PCOS (polycystic ovary syndrome), berberine has demonstrated a notable ability to improve the lipid profile, specifically by increasing HDL cholesterol and reducing total and LDL cholesterol levels [16]. Additionally, a systematic review of clinical trials highlighted berberine's broader metabolic benefits, including enhanced insulin sensitivity and lipid profile improvements, making it a potential therapeutic agent for managing obesity-related dyslipidemia and metabolic disorders.

2.2. Berberine's influence on adipose tissue remodeling

2.2.1. Preclinical studies

Numerous preclinical studies have demonstrated berberine's potential to induce browning of white adipose tissue (WAT) and activate brown adipose tissue (BAT), mechanisms that hold promise for combating metabolic disorders. Berberine has been shown to increase the expression of thermogenic markers such as UCP1, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), carnitine palmitoyltransferase (CPT1), and nuclear respiratory factor 1 (NRF1) in WAT, promoting the formation of beige adipocytes in diet-induced obese mice [11, 14]. This browning effect is accompanied by the downregulation of lipogenic genes in WAT, reducing fat storage, and upregulation of oxidative genes, which enhance mitochondrial formation and thermogenesis [14].

The molecular mechanisms underlying these effects involve the activation of key pathways, including the AMPK/SIRT1 signaling axis and the AMPK–PRDM16 axis, which are critical for WAT browning and BAT activation. Sirtuin 1 (SIRT1), a protein deacetylase, plays a pivotal role in modulating enzymes and transcription factors involved in mitochondrial function and energy expenditure. Additionally, berberine promotes DNA demethylation at the PRDM16 promoter, facilitating BAT differentiation and thermogenesis [17]. Berberine also enhances the secretion of fibroblast growth factor 21 (FGF21), a hormone linked to thermogenic and metabolic regulation, by modulating molecular clock components in BAT [18]. Notably, berberine has been found to increase glucose uptake in BAT, further indicating enhanced thermogenic activity [14].

Animal studies further support these findings. In high-fat diet-fed rats, berberine significantly upregulated the expression of browning markers (UCP1, PGC-1α, and cell death-inducing DFFA-like effector A, or CIDEA) in inguinal WAT, while also improving lipid profiles and metabolic parameters. These effects suggest berberine not only promotes adipocyte browning but also ameliorates obesity-induced dyslipidemia [19].

2.2.2. Clinical studies

Although clinical research on berberine's effects on BAT and WAT remains limited, available studies corroborate the findings from preclinical models. Berberine supplementation in mildly overweight individuals has been shown to increase BAT activity and mass, improve insulin

sensitivity, and reduce body weight. These effects are attributed to the upregulation of brown adipogenic genes and enhanced thermogenesis, linking berberine administration to BAT activation in humans [17]. Moreover, berberine's activation of BAT has been associated with improvements in metabolic profiles, including reductions in serum glucose and lipid levels, highlighting its potential as an adjunct therapy for metabolic syndrome and obesity-related conditions [14, 20]. The role of fibroblast growth factor 21 (FGF21) in clinical outcomes is noteworthy. Berberine has been shown to increase hepatic FGF21 expression, which contributes to WAT browning and enhances the thermogenic program of BAT [14].

2.3. The effects of berberine on glycemic control and insulin sensitivity

2.3.1. Preclinical studies

Numerous preclinical studies have demonstrated the potential of berberine to improve glycemic control, reduce insulin resistance, and modulate key metabolic pathways. For instance, berberine was shown to enhance the LKB1/AMPK/PGC1α pathway in fructose-fed mice, leading to improved insulin sensitivity, reduced fasting insulin levels, and increased hepatic glycogen content [21]. Similarly, BBR suppressed hepatic gluconeogenesis by inhibiting glucose production and gluconeogenic gene expression in hepatocytes, particularly under the influence of lactate and glucagon [22]. The mechanism underlying this suppression involves the downregulation of cAMP levels, inhibition of CREB phosphorylation, and activation of phosphodiesterase (PDE), reducing gluconeogenic gene transcription [22, 23]. These effects collectively reduce hepatic glucose output, a crucial step in ameliorating hyperglycemia.

In other studies, berberine modulated gut microbiota to reduce the production of branched-chain amino acids associated with insulin resistance, thereby improving glucose tolerance and reducing adipose inflammation in high-fat diet-fed mice [24]. Additionally, in diabetic mouse models such as ob/ob and streptozotocin (STZ)-induced diabetic mice, BBR lowered blood glucose levels and enhanced insulin and glucose tolerance [23]. These mouse models mimic obesity-induced and type 1 diabetes-like conditions, respectively, and are valuable tools for studying the molecular mechanisms of diabetes. Notably, berberine increased insulin sensitivity in adipocytes by activating the PI3K/Akt pathway and inhibiting the serine phosphorylation of insulin receptor substrate-1 (IRS-1), mechanisms critical for enhancing insulin signaling [25].

Emerging derivatives of berberine have also shown promise. For example, a novel compound, 9-N-berberine, demonstrated potent hypoglycemic activity by improving insulin sensitivity and reducing body weight in obese diabetic mice [26]. Collectively, these preclinical findings emphasize BBR's multifaceted role in combating insulin resistance through hepatic, muscular, and adipose tissue pathways.

2.3.2. Clinical studies

Clinical trials further validate berberine's efficacy in improving humans' glycemic parameters and insulin sensitivity. A randomized controlled trial demonstrated that berberine supplementation significantly reduced fasting glucose, insulin levels, and HOMA-IR (an indicator of insulin resistance) in overweight individuals with impaired fasting glucose. The

study also reported reductions in visceral adipose tissue and fat mass, with no adverse events, underscoring its safety and therapeutic potential [27]. Similarly, a meta-analysis of randomized controlled trials revealed that berberine decreased BMI, waist circumference, and fasting glucose levels in patients with metabolic syndrome, further supporting its role in managing obesity and improving insulin sensitivity [8].

Berberine has also been shown to provide benefits in conditions like polycystic ovary syndrome (PCOS). For example, a 2020 review summarizing five clinical trials reported that BBR reduced insulin resistance in theca cells by increasing GLUT-4 expression in the ovaries, thereby enhancing glucose uptake and improving ovulation rates. Additionally, berberine supplementation normalized fasting glucose, insulin levels, and HOMA-IR in women with PCOS, highlighting its role in reducing hyperinsulinemia and associated androgen excess [16]. Another clinical study comparing berberine to Gymnema sylvestre in obese patients highlighted berberine's superior effects on body weight reduction, glucose tolerance improvement, and modulation of adipokines related to insulin sensitivity [28].

2.4. Anti-inflammatory effects of berberine in obesity

2.4.1. Preclinical studies

Berberine has demonstrated significant anti-inflammatory effects through its ability to inhibit the production of pro-inflammatory molecules and cytokines, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α). The mechanism underlying these effects involves the deactivation of the nuclear factor (NF)-κB pathway, where berberine prevents the degradation of Iκ-Bα, an inhibitor of NF-κB. By restricting the release and nuclear translocation of NF-κB p65, as well as reducing its DNA-binding activity, berberine suppresses the activation of inflammatory genes [29].

These anti-inflammatory properties have been extensively studied in the context of obesity-induced inflammation. Preclinical investigations indicate that berberine modulates adipose tissue macrophage recruitment and polarization, contributing to its therapeutic effects. For instance, Ji-Won Noh et al. demonstrated that high-fat diet-fed mice treated with berberine exhibited significant reductions in body weight, fat accumulation, and inflammatory markers such as TNF-α and chemokines, while also showing an increase in anti-inflammatory M2 macrophages [30].

Similarly, Li et al. highlighted berberine’s ability to alleviate high-fat diet-induced metabolic syndrome through modulation of gut microbiota and inhibition of liver inflammation, establishing a direct link between its anti-inflammatory effects and improved metabolic health [31].

Further insights into berberine’s mechanisms were provided by Dan Li et al. who found that berberine activated Sirtuin 3 (SIRT3), thereby reducing macrophage infiltration and pro-inflammatory responses in adipose tissue, mitigating obesity-related complications [32]. Neyrinck et al. also reported that berberine improved gut barrier function and reduced hepatic

inflammation by modulating gut microbiota, emphasizing its prebiotic effects in lowering inflammatory markers [33].

2.4.2. Clinical studies

Clinical evidence supports the anti-inflammatory benefits of berberine in the context of obesity. A systematic review by Xiong et al. demonstrated significant reductions in anthropometric indices, including body mass index (BMI) and waist circumference, as well as inflammatory markers like C-reactive protein (CRP) in individuals supplemented with berberine [8]. Vahedi-Mazdabadi et al. confirmed these findings in a meta-analysis, showing dose-dependent reductions in IL-6 and TNF-α levels with berberine supplementation at doses below 1000 mg/day, emphasizing its role in managing obesity-related inflammation [34].

Lin et al. reported that berberine treatment improved metabolic functions in obese individuals by polarizing macrophages toward the anti-inflammatory M2 phenotype and reducing pro-inflammatory cytokines in adipose tissue [35]. These effects were mirrored in findings from Asbaghi et al., who noted a significant impact on CRP levels, suggesting systemic anti-inflammatory effects [36].

2.5. Effects of berberine on gut microbiota

2.5.1. Preclinical studies

Preclinical studies provide robust evidence that berberine exerts its therapeutic effects in obesity by modulating the gut microbiota. For instance, research conducted on mice with high-fat diet-induced obesity demonstrated that berberine not only alleviated metabolic syndrome but also inhibited liver inflammation by regulating the gut microbiota composition. This regulation included an increase in beneficial bacteria and a reduction in pro-inflammatory microbial metabolites, such as lipopolysaccharides, which contribute to systemic inflammation [31].
Further studies highlight the role of berberine in enhancing the diversity of gut microbiota and promoting the growth of specific beneficial taxa, such as Akkermansia and Bifidobacterium. These microbes are known to improve gut barrier function and reduce systemic inflammation, which are critical factors in combating obesity and metabolic disorders [37]. Additionally, berberine's effects on tryptophan metabolism were shown to alleviate intestinal barrier dysfunction and decrease inflammatory responses in glucolipid metabolism disorders [38]. Innovative delivery systems, such as colon-specific nanoparticles, have further amplified the therapeutic potential of berberine by enhancing its direct interaction with the gut microbiota. These systems demonstrated superior efficacy in reducing weight gain and improving insulin sensitivity compared to traditional berberine formulations [39]

2.5.2. Clinical studies

Clinical research corroborates the preclinical findings, demonstrating that berberine effectively modulates gut microbiota and improves metabolic health in humans. A pivotal study showed that berberine's cholesterol-lowering effects were closely linked to its ability to

alter gut microbiota composition, particularly by increasing the relative abundance of beneficial genera such as Blautia and Alistipes. These findings highlight the gut microbiota's essential role in mediating berberine's lipid-lowering and anti-inflammatory properties [40]. Moreover, clinical trials have demonstrated that berberine supplementation enhances gut microbiota diversity and promotes the proliferation of short-chain fatty acid-producing bacteria, which are integral to maintaining gut homeostasis and reducing systemic inflammation. These microbial shifts are associated with significant improvements in markers of metabolic health, including reduced body weight and improved lipid profiles [37].

2.6. Effect of berberine on anthropometric parameters

2.6.1. Preclinical studies

Evidence from preclinical models highlights berberine's ability to reduce body weight, fat mass, and associated inflammation. For instance, animal studies have shown that berberine significantly decreases body weight and visceral fat, primarily through mechanisms like improved insulin sensitivity and regulation of lipid metabolism [14]. These foundational studies elucidate the biochemical pathways underlying berberine's effects, establishing a basis for its therapeutic potential, though anthropometric outcomes are more directly assessed in human studies.

2.6.2. Clinical studies

Clinical research has further validated berberine's impact on obesity-related metrics, including body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), and visceral fat reduction. A meta-analysis of randomized controlled trials (RCTs) demonstrated significant reductions in BMI (weighted mean difference [WMD]: -0.47 kg/m^2), WC (-1.08 cm), and WHR following berberine supplementation [36]. Another dose-response meta-analysis emphasized that prolonged berberine treatment (e.g., >12 weeks) achieved more substantial reductions in WC (-2.75 cm) and BMI, likely linked to improvements in lipid profiles and inflammation [8]

Interestingly, berberine appears to induce fat redistribution, particularly targeting visceral fat mass, even in cases where overall weight loss is minimal [16]. Systematic reviews also confirm improvements in WHR, with modest but clinically relevant reductions in BMI and body weight [41]. Furthermore, clinical trials underscore that berberine is more effective when paired with lifestyle interventions, such as dietary and exercise modifications. One study reported significantly greater reductions in weight and WC in participants combining lifestyle changes with berberine supplementation compared to those with lifestyle changes alone [42].

3. Bioavailability

Berberine, a quaternary ammonium isoquinoline alkaloid, exhibits diverse pharmacological effects including antimicrobial, anti-inflammatory, and antidiabetic properties. However, its clinical utility is significantly limited by poor oral bioavailability, primarily due to low solubility, poor intestinal absorption, rapid first-pass metabolism, and efflux mediated by P-glycoprotein (P-gp) [43]. Recent advances in pharmaceutical formulation and delivery systems have been instrumental in addressing these bioavailability challenges.

Studies have highlighted that first-pass metabolism and limited membrane permeability significantly restrict the systemic absorption of berberine. Innovations such as lipophilic metabolite development, salt/ion-pair complexation, and the incorporation of P-gp inhibitors have been explored to enhance berberine's pharmacokinetic profile [44]. Furthermore, novel delivery systems, including liposomes, nanosuspensions, and liquid crystalline nanoparticles, have significantly improved berberine's solubility and absorption. For instance, liposomal encapsulation and nanosuspension formulations improved berberine's dissolution rate and bioavailability by up to 27-fold in experimental models [45].

Clinical investigations have further validated these enhancements. A novel food-grade berberine delivery system (LipoMicel®) demonstrated up to a six-fold increase in systemic absorption compared to standard formulations in human volunteers [46]. Similarly, a self-microemulsifying drug delivery system (SMEDDS) achieved a 1.63-fold increase in bioavailability while maintaining stability and pharmacological efficacy [47].

Additional strategies, such as the utilization of rectal delivery routes, have shown promise by bypassing hepatic first-pass metabolism. This approach increased berberine bioavailability from 0.26% (oral) to over 24% (rectal) in preclinical studies [48]. Moreover, hyaluronic acid-based liposomal systems and MgAl hydrotalcite carriers have been identified as innovative approaches to enhance intestinal absorption and systemic availability, offering therapeutic benefits for conditions like diabetes and cardiovascular diseases [49, 50].

4. Safety, tolerance, and side effects

Several clinical and preclinical studies highlight that berberine generally exhibits a favorable safety profile when used within standard dosage ranges. Commonly reported adverse effects are predominantly gastrointestinal, including diarrhea, constipation, and mild gastrointestinal discomfort. These side effects are dose-dependent and transient, typically resolving upon discontinuation or dose adjustment [51, 52]. These findings are corroborated by a systematic review of randomized controlled trials, which noted no significant increase in adverse events compared to placebo, even when berberine was used adjunctively with other medications [53].

Notably, berberine demonstrates a low risk of hepatotoxicity and nephrotoxicity, as evidenced by preclinical toxicological assessments. In animal models, parameters such as liver enzymes, renal function markers, and hematological profiles remain within normal ranges following berberine administration [54]. Furthermore, clinical reviews emphasize its minimal systemic toxicity, attributing this to its limited bioavailability and primary action at the gastrointestinal level [55].

Despite these positive attributes, emerging evidence suggests a need for caution in individuals with specific conditions. For instance, berberine may interfere with cytochrome P450 enzymes, potentially altering the pharmacokinetics of concurrently administered drugs [55]. Additionally, the safety of long-term high-dose berberine usage requires further investigation through high-quality longitudinal studies.

5. Berberine dosage for weight loss

Studies indicate that a daily dose of 500 mg of berberine effectively modulates gut microbiota diversity, improves glucose accumulation, and regulates cholesterol absorption. These mechanisms collectively contribute to weight reduction [15]. Similarly, meta-analyses of randomized controlled trials report significant reductions in body mass index and waist circumference with berberine supplementation. The dosage-response evaluations reveal that dosages ranging from 300 to 1,000 mg/day administered over weeks to months are associated with these benefits [8].

Additionally, advanced formulations like berberine phospholipid complexes have been explored to enhance bioavailability and metabolic effects. One study found that a dose of 1,100 mg/day (550 mg twice daily) improved body composition and reduced visceral adipose tissue in overweight individuals over two months, supporting its role in weight management [27]. Furthermore, evidence from other clinical trials suggests that berberine is generally safe and well-tolerated, with mild gastrointestinal side effects observed in higher doses [56].
In conclusion, berberine supplementation at doses between 500 and 1,000 mg/day is effective and safe for weight management, with higher efficacy observed when used in enhanced formulations or alongside dietary and lifestyle modifications.

6. Summary

This study reviews the therapeutic potential of berberine in obesity treatment, focusing on its mechanisms of action and clinical evidence. Obesity, a condition linked to metabolic syndrome, cardiovascular diseases, and other complications, requires innovative approaches beyond conventional treatments. Berberine exhibits a broad spectrum of anti-obesity effects, including improving lipid profiles, enhancing insulin sensitivity, and promoting energy metabolism. It also influences gut microbiota and anti-inflammatory pathways, contributing to its effectiveness. Despite its low oral bioavailability, advancements in delivery systems have improved its clinical application. The findings affirm berberine's role as a supportive agent in obesity management, especially when combined with lifestyle interventions, offering a safe and effective alternative for addressing this pressing health issue.

Disclosure

Author's contribution

Conceptualization: Katarzyna Kamińska-Omasta; Methodology: Bartosz Omasta; Software: Szymon Przemysław Stolarczyk; Check: Kuba Borys Romańczuk and Daria Rybak; Formal analysis: Kinga Furtak and Olga Krupa; Investigation: Paulina Dorota Pietrukaniec and Magdalena Agata Czerska; Resources: Zofia Martyna Wójcik and Bartosz Omasta; Data curation: Daria Rybak; Writing - rough preparation: Olga Krupa; Writing - review and editing: Katarzyna Kamińska-Omasta and Kinga Furtak; Visualization: Zofia Martyna Wójcik and Szymon Przemysław Stolarczyk; Supervision: Katarzyna Kamińska-Omasta; Project administration: Paulina Dorota Pietrukaniec and Kuba Borys Romańczuk; Receiving funding - no specific funding.
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