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REVIEW

Advances in Nano-Phototherapy for Targeted Fat Reduction: From Mechanisms to Clinical Translation in Obesity

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Background: Obesity is a global public health concern, and traditional surgical interventions such as liposuction, although effective, carry risks of trauma and complications. Non-invasive phototherapies, including photobiomodulation therapy (PBMT), photodynamic therapy (PDT), and photothermal therapy (PTT), have emerged as promising alternatives.

Methods: This narrative review synthesizes current literature on phototherapy-based fat reduction. A PubMed search was conducted using the terms ("photosensitive material" OR "photodynamic therapy" OR "photothermal" OR "photobiomodulation") AND ("lipolysis" OR "fat reduction" OR "body contour"). Of 105 studies meeting inclusion criteria, 80 were selected for detailed analysis, focusing on PBMT, PDT, and PTT in non-invasive fat reduction.

Results: PDT induces adipocyte apoptosis and tissue remodeling via ROS generated by photosensitizers; PTT applies near-infrared light to heat adipose tissue, promoting fat cell death and enhancing local metabolic activity; PBMT stimulates mitochondrial activity, accelerating lipolysis and metabolic processes. Some studies indicate that the use of nanomaterials may modestly enhance targeting and therapeutic efficacy.

Conclusion: Non-invasive phototherapy shows great potential in obesity management, and the integration of nanomaterials may further enhance targeting and therapeutic efficacy, enabling safer and more efficient fat reduction. Future studies should optimize phototherapy parameters and explore the synergistic effects of nanomaterials and personalized intervention strategies.

Keywords: nanotechnology, non-invasive techniques, obesity, photobiomodulation, photodynamic therapy, photothermal therapy

Introduction

Obesity, a global epidemic associated with metabolic disorders, diabetes, and cardiovascular diseases, poses a major public health concern. Conventional treatments, such as appetite suppressants and fat absorption inhibitors, often yield limited efficacy and notable side effects.[1,2] Invasive procedures like liposuction effectively remove fat but cause pain, bleeding, and prolonged recovery.[1,3] With rising demand for safer alternatives, non-surgical body contouring methods—cryolipolysis,[4,5] radiofrequency, focused ultrasound, and low-level laser therapy (LLLT)—have gained popularity for their minimal invasiveness and satisfactory results in localized fat reduction.[6,7] Each method acts through distinct mechanisms: radiofrequency promotes collagen remodeling and fat metabolism by dermal heating;[8] cryolipolysis induces adipocyte apoptosis through controlled cooling;[5] ultrasound mechanically disrupts fat cells;[9] and LLLT modulates cellular metabolism to promote lipolysis and reduce fat cell volume.[10,11] Laser-assisted lipolysis (LAL), combining photothermal fat emulsification with skin tightening, especially in areas with dense tissue.[12] Collectively, these techniques provide effective, safe, and non-surgical solutions for localized fat reduction and metabolic improvement.

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Recently, phototherapy has shown great potential in this field, promoting non-invasive lipolysis, adipocyte apoptosis, and metabolic regulation.[13] However, a systematic understanding of its mechanisms and applications in fat reduction remains lacking. This review aims to comprehensively summarize current research on photothermal therapy (PTT), photodynamic therapy (PDT), and photobiomodulation therapy (PBMT) in fat reduction, and explore their clinical potential in obesity management. In particular, the incorporation of nanotechnology has further expanded the scope of phototherapy by enhancing light absorption, targeted energy delivery,[14,15] and treatment precision, offering new possibilities for safe and efficient fat reduction.

Advances of Phototherapy in Clinical Medicine

In vitro Studies

In vitro studies support the fat-lipolysis effects of light therapy. Fat cells were exposed to specific wavelengths and power intensities, and their lysis rates were assessed. The results revealed that light therapy induced cell membrane rupture and promoted fat cell lysis, with the lysis rate positively correlated with light dose and wavelength, thus supporting its potential clinical application.

In PDT cell experiments, researchers evaluated the effects of various photosensitizers on adipocyte differentiation. The findings demonstrated that Tetraphenylethene tetramethylthienothiophene-2-one (TTMN) and Methylated tetraphenylethene tetramethylthienothiophene-2-one (MeTTMN) specifically targeted lipid droplets in mature fat cells and efficiently produced reactive oxygen species (ROS) under light exposure, thereby inducing adipocyte apoptosis.[15] Additionally, in HUTU-80 (human duodenal cells) and HEK 293 (human embryonic kidney cells) transfected cells, the uptake and ROS generation capabilities of Oleic acid-poly (ethylene glycol)-chlorin e6 (OA-PEG-Ce6, OPC) were assessed. The results indicated that OPC exhibited superior cell uptake efficiency compared to other photosensitizers and could effectively generate ROS, further promoting cell apoptosis.[16]

A recent PTT study designed a resveratrol nanoparticle-loaded photothermal-responsive alginate hydrogel (SDAR) for anti-obesity treatment. In 3T3-L1 preadipocytes, SDAR exhibited excellent photothermal performance and biocompatibility, significantly reducing intracellular ROS and inflammatory cytokine expression. Moreover, it inhibited lipid accumulation as shown by Oil Red O staining and downregulated adipogenic markers, suggesting suppression of adipocyte differentiation and promotion of fat metabolism.[17]

The subsequent in vitro studies provide additional evidence supporting the efficacy of PBMT in fat reduction and adipocyte modulation. In a pigskin model, hydrogel containing CuS nanoparticles was administered and exposed to near-infrared (NIR) irradiation (0.4 W/cm^2 for 5 minutes). The findings revealed that subcutaneous fat temperature rose to 40°C, while the skin surface temperature remained below 44°C, preventing skin burns.[18] A similar experiment in human subcutaneous adipocytes demonstrated that photothermal therapy enhanced lipolysis, using Oil Red O staining, which revealed smaller lipid droplets, increased free fatty acids (FFA) release, and transferase-mediated dideoxyuridine triphosphate-biotin nick end labeling (TUNEL) staining indicating an increase in adipocyte apoptosis. The increased expression of uncoupling protein 1 (UCP1) protein confirmed the conversion of white adipocytes into brown adipocytes.[18] In a 3T3-L1 cells adipocyte model, nanoparticles were used to deliver molecules such as Rosi and Resveratrol, effectively promoting adipocyte browning. This led to upregulation of UCP-1 and Peroxisome proliferator-activated receptor gamma coactivator-1 alpha(PGC1α) expression and increased energy expenditure, further supporting the effectiveness of white adipose tissue (WAT) browning.[14]

In multiple experiments, the combined application of PTT and PDT demonstrated significant effects in fat removal. Optical Coherence Tomography (OCT) technology was used to monitor the impact of PTT and PDT on adipocytes, utilizing fat tissue samples obtained from human surgical waste. The results revealed that by optimizing light source and dye combinations, fat tissue could be selectively destroyed under controlled temperatures.[19] The results demonstrated that treatment with Indocyanine Green (ICG) dye and 808 nm laser at 37°C was most effective, rapidly and deeply damaging adipocytes.[20]

Animal Studies

In PDT research, methylene blue (MB) was used as a photosensitizer to generate ROS under 670 nm light, selectively ablating the mouse duodenal mucosa while sparing surrounding tissues.MB is safe, rapidly excreted, and non-toxic in the absence of light.[21] In a mouse model with obesity, photosensitizer-light treatment significantly reduced body weight, fat thickness, and blood glucose, with smaller lipid droplets in adipocytes and increased apoptosis.[15] In a mouse model with obesity and type 2 diabetes, OPC combined with endoscopic laser irradiation in OPC-PDT treatment led to significant reductions in body weight, blood glucose, lipid levels, and gastric inhibitory polypeptide (GIP), highlighting its targeted effect on K cells.[16] Building on these findings, an ultra-small hybrid nanoparticle platform (Pep-PPIX-Baic NPs) was recently developed to enhance the precision and efficacy of PDT. This nanoplatform integrates the targeting peptide CKGGRAKDC for adipose tissue recognition, the photosensitizer protoporphyrin IX (PPIX) and Fe^{3}+ for improved photodynamic efficiency, and baicalin as a bioactive compound to modulate lipid metabolism. These nanoparticles exhibit excellent biocompatibility, high photothermal stability, and efficient accumulation in adipose tissue, ultimately achieving safe and adipose-specific anti-obesity effects through precise light-activated intervention.[22]

In a series of animal studies related to PBMT, phototherapy techniques, including LLLT and PTT, exhibited substantial anti-obesity effects, particularly in fat reduction and metabolic regulation. In one experiment, male rats were divided into four groups, receiving brilliant green (BG) and light-emitting diode (LED) irradiation, ICG and laser irradiation, or individual BG or ICG treatments. The results showed that combined dye and light treatment resulted in significant damage to adipocyte membranes, with complete adipocyte replacement by fibrous tissue after 14 days, indicating effective induction of adipocyte necrosis.[23] Another study using 830 nm LLLT combined with exercise further confirmed the regulatory effect of LLLT on lipid metabolism. After 8 weeks of swimming training, the group receiving both laser and exercise treatment exhibited substantial reductions in total cholesterol, triglycerides (TG), and adipose tissue mass, demonstrating a synergistic effect of LLLT in regulating lipid metabolism and improving adipose tissue function.[24]

Studies using 660 nm and 808 nm lasers to treat subcutaneous abdominal fat in female Wistar rats showed that a 5 J/cm^2 dose of red light significantly reduced fat thickness without adverse effects on liver biochemical markers. However, infrared light at specific doses may negatively impact lipid metabolism, highlighting the need for treatment optimization.[25] In a high-fat diet-induced insulin-resistant mouse model, PBMT for abdominal irradiation significantly reduced plasma FFA and TG, with increased adipocyte size, suggesting suppressed lipolysis and improved insulin sensitivity.[26] Combined PDT and PTT treatments in rats also showed promising fat removal effects, with ICG injection and laser irradiation inducing significant adipocyte necrosis and minimal skin damage, indicating selective destruction of adipocytes.[27]

Recent advances in nanotechnology have enabled the development of diverse photothermal nanoplatforms for noninvasive, localized, and biocompatible management of obesity. A variety of nanomaterials, including Prussian blue nanoparticles (PBNPs),[28] gold nanorods(AuNR),[29] polypyrrole-based composites, and protein- or polysaccharide-derived carriers,[30] have been engineered to achieve precise photothermal conversion, adipose tissue targeting, and sustained local retention. Prussian blue nanoparticle–silk fibroin hydrogels exhibit high photothermal efficiency and catalytic stability, enabling mild yet effective heat generation under NIR irradiation.[28] Similarly, pufferfish-shaped polypyrrole–lecithin nanoparticles synthesized via microwave-assisted self-assembly demonstrate exceptional photothermal conversion and fat-tissue selectivity due to their unique morphology and surface amphiphilicity.[30] Gold nanorod–antibody conjugates further enhance targeting accuracy by binding specific adipocyte surface receptors, achieving controllable fat ablation with minimal systemic exposure.[29] Collectively, these nanomaterials combine superior photothermal responsiveness, biodegradability, and tunable physicochemical properties, providing a versatile platform for localized obesity intervention.

Integration of photothermal nanomaterials into advanced delivery systems further improves therapeutic precision and patient safety. Effervescent microneedle (EMN) patches incorporating chitosan nanoparticles and ICG enable efficient transdermal delivery and synergistic photothermal fat degradation, while maintaining excellent skin compatibility.[31] Likewise, cationic albumin-based nanoparticles loaded with rosiglitazone(RSG) and embedded in thermosensitive

hydrogels combine photothermal activation with pharmacological stimulation, promoting local fat reduction and metabolic normalization without systemic toxicity.[32] These systems achieve controlled release, deep tissue penetration, and localized activation under NIR irradiation, ensuring both efficacy and biocompatibility. Together, these studies underscore the promise of nanocarrier-enhanced photothermal technologies as next-generation strategies for precise, minimally invasive, and safe management of obesity and related metabolic disorders (Table 1 and Figure 1).

Clinical Efficacy Evaluation

Currently, light therapy is supported by substantial clinical evidence for its effectiveness in non-invasive fat reduction. Research demonstrates that this approach effectively reduces fat thickness and enhances body contouring at the treatment site. Data from multiple clinical trials reveal that patients report reduced fat thickness and improved contour uniformity, with consistently high levels of satisfaction (Table 2).

Photothermal Therapy

PTT achieves fat reduction by inducing localized adipocyte apoptosis through controlled heating (42–47 °C) using lasers operating at wavelengths between 980 nm and 1320 nm. Clinical trials have confirmed that this approach effectively reduces subcutaneous fat thickness and improves contour uniformity, with overall patient satisfaction typically exceeding 80%.[12] A multicenter clinical study using a 1060 nm semiconductor laser reported over 90% satisfaction and minimal invasiveness, allowing patients to resume normal activity immediately after treatment.[34] In trials involving 1064 nm lasers with integrated cooling systems, reductions in abdominal fat thickness and waist circumference were confirmed by ultrasound assessments.[35,36]

Combination and wavelength optimization studies have demonstrated additional benefits. For instance, a 755 nm picosecond laser combined with a 1060 nm laser significantly improved neck laxity and contour definition,[37] while the 1064 nm Nd:YAG laser effectively reduced flank fat and enhanced skin tightening, yielding >90% patient satisfaction.[38] The subdermal photothermal technique Endolaser (Endolift) has also shown promise in facial contouring, fat reduction, and skin rejuvenation. A scoping review that included 26 studies—only one being an randomized controlled trial (RCT)—reported high satisfaction rates and noticeable aesthetic improvements, though the overall evidence quality was low.[39] Collectively, PTT demonstrates consistent efficacy and favorable safety for localized fat reduction and contour enhancement. However, the lack of standardized energy parameters and long-term follow-up underscores the need for high-quality RCTs to confirm durability and optimize protocols.

Photobiomodulation

PBMT, employing LLLT or LED light primarily in the red to NIR spectrum (532–850 nm), promotes adipocyte lipolysis and tissue remodeling through mitochondrial activation. Clinical trials and reviews have provided increasing evidence of its efficacy and safety in non-invasive fat reduction.

In a randomized controlled study of 90 women, red and NIR LED therapy significantly reduced abdominal circumference and fat thickness, accompanied by increased collagen deposition and macrophage infiltration, suggesting simultaneous lipolytic and remodeling effects. The addition of a topical agent provided no extra benefit, and all participants reported high satisfaction without adverse events.[40] Another RCT involving 54 adolescents with obesity compared PBMT with non-contact radiofrequency (NcRF), showing that PBMT achieved greater reductions in subcutaneous fat thickness and waist-to-hip ratio, whereas NcRF exhibited moderate effects.[41] Similarly, a six-week, biweekly LLLT regimen resulted in reduced body fat and improved quality of life without side effects,[42] and repeated 635 nm LLLT sessions produced progressive reductions in waist-to-hip ratio.[43]

Laser acupuncture represents an innovative PBMT application. A RCT demonstrated that laser acupuncture, including noninvasive stimulation of auricular hunger and stomach points as well as body acupoints, significantly reduced postpartum body mass index (BMI) and body fat percentage (BFP), with BMI decreasing from 33.62 ± 3.19 to 26.90 ± 2.29 and BFP from 36.94 ± 2.65% to 35.75 ± 3.05% (both $P < 0.001$), although its long-term effects remain to be further validated.[54] Another RCT combining laser acupuncture with a low-calorie diet among postmenopausal women yielded significant improvements in BMI, insulin resistance, and depressive symptoms.[55]

Table 1 In Vitro and Animal Model Studies of Phototherapy

Study Type	Model System	Intervention	Main Findings	Ref.
In vitro + animal study	IEC-6 intestinal epithelial cells; HFD-fed C57BL/6 mice	PDT (Methylene Blue + 670 nm)	Reduced body weight and blood glucose, enhanced insulin sensitivity, no significant complications	[21]
In vitro + animal study	3T3-L1 adipocytes; obese BALB/c mice	PDT: AIE photosensitizer (TTMN / MeTTMN)	Induced lipid peroxidation and cell death, significantly reduced fat, high safety	[15]
In vitro + animal study	3T3-L1 adipocytes; HFD-fed C57BL/6 mice	PDT: Pep-PPIX-Baic ultrasmall hybrid nanoparticles	Synergistically induced adipocyte apoptosis and browning, markedly decreased adipose volume and body weight, enhanced energy expenditure, and exhibited no apparent toxicity	[22]
In vitro + animal study	HUTU-80 and GPR119-HEK293 cells; obese + T2DM mice	K cell-targeted PDT (Oleic Acid-PEG-Ce6 + 670 nm)	Selectively induced K cell death, decreased GIP; ~47% reduction in mouse weight and fat, improved glycemia	[16]
In vitro + animal study	3T3-L1 cells and obese mice under CAP stimulation	PDT: CAP-responsive nanoparticles (RANP; co-delivery of LDH and NADH)	Amplified ROS generation, promoted lipolysis, apoptosis, and browning; reduced adiposity and improved hepatic lipid deposition	[33]
In vitro study	Subcutaneous fat from obese rats	PDT/PTT: ICG + 808 nm laser	ICG-mediated photothermal/photodynamic therapy effectively disrupted adipose tissue	[27]
In vitro study	Human adipose tissue slices	PDT/PTT (BG 442/597 nm; ICG 808 nm)	Induced lipolysis and structural damage; significant alteration of cellular architecture	[20]
In vitro + animal study	Nanomaterial-mediated cellular and animal models (review)	PTT: targeted inhibition of white adipose tissue angiogenesis; promotion of WAT browning; nanomaterial-mediated photothermal lipolysis	Targeted nanoplatforms enhanced drug accumulation and photothermal lipolysis efficiency	[14]
In vitro study	3T3-L1 preadipocytes	Photothermal hydrogel: Sodium alginate-based (SDAR) containing resveratrol nanoparticles	Inhibited adipogenesis and inflammation, upregulated UCP1 expression, showed antioxidant and anti-inflammatory effects, and exhibited excellent biocompatibility	[17]
In vitro + in vivo combined study	3T3-L1 adipocytes; HFD-induced obese mice	Photothermal-nanocatalytic system: Prussian blue nanoparticle–silk fibroin hydrogel (PBNP@SF) + 808 nm mild NIR irradiation	Promoted adipose browning and lipid droplet degradation, mitigated oxidative stress and inflammation, induced 9.78% weight loss, 53.95% subcutaneous and 65.37% visceral fat reduction, with high safety	[28]
In vitro + in vivo combined study	3T3-L1 adipocytes; HFD-induced obese mice	Photothermal-autophagy system: Foam microneedle-mediated chitosan oligosaccharide nanoparticle delivery + ICG-based photothermal therapy	Induced lipophagy and adipose browning, reduced body weight by ~38%, and improved metabolic function	[31]
In vitro + in vivo combined study	3T3-L1 adipocytes; HFD-induced obese mice	Photothermal therapy: Soy lecithin–polypyrrole "pufferfish-like" nanoparticles under NIR irradiation	Promoted adipose browning and apoptosis, decreased body weight and serum lipids, demonstrated strong adipose-targeting ability and safety	[30]
In vitro + in vivo combined study	Human adipocytes; HFD-induced obese mice	Targeted photothermal therapy: Gold nanorod–PPARγ monoclonal antibody conjugates under NIR irradiation	Specifically targeted adipocytes, induced apoptosis, markedly reduced adipose thickness, and showed good safety	[29]
In vitro + in vivo combined study	3T3-L1 adipocytes; HFD-induced obese mice	Photothermal–pharmacologic therapy: Cationic albumin nanoparticles loaded with rosiglitazone + IR780 thermosensitive hydrogel	Enhanced adipose browning and energy expenditure, reduced body weight and lipid levels, and ameliorated metabolic abnormalities and hepatic steatosis	[32]
Animal study	Male Wistar rats	PBM: low-level laser therapy + exercise	Improved lipid profile and glycogen storage; LLLT enhanced exercise-induced metabolic benefits	[24]
In vitro study	Subcutaneous fat from female Wistar rats	PBM: 660 nm / 808 nm laser (3.3–5 J/cm^2, 5 weeks)	660 nm red light significantly reduced fat thickness, no liver function abnormalities	[25]
In vitro + animal study	3T3-L1 adipocytes; obese and diabetic mice	PBMT (635 nm, 8 J/cm^2, 10 weeks)	Suppressed lipolysis, improved insulin resistance; effect dependent on ROS-AKT pathway	[26]
In vitro study	Subcutaneous adipocytes from obese women	PBM: LED (630 nm + 850 nm)	Activated mitochondrial metabolism and lipolysis, enhanced apoptosis	[19]

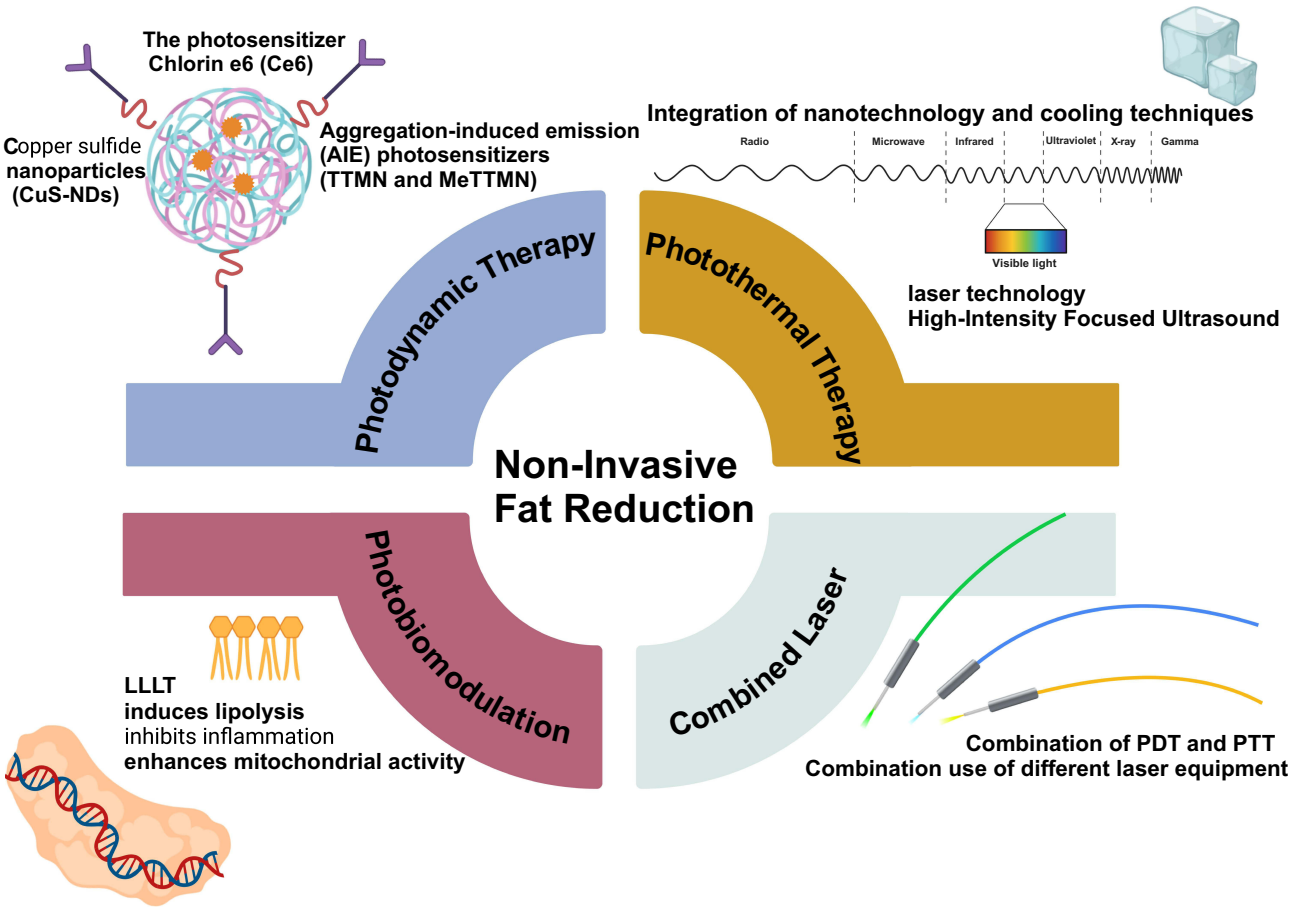

Figure 1 Background and classification of phototherapy in non-invasive lipolysis techniques.

Mechanistic and combination studies have reinforced these findings. PBMT with red and infrared light in obese women induced adipocyte apoptosis and decreased fat accumulation,[29] while dual-wavelength irradiation (1060 nm + 635 nm) significantly reduced abdominal and jawline fat with a 96% satisfaction rate.[46] Multi-wavelength PBMT (red, infrared, and blue light) achieved non-invasive abdominal fat reduction without adverse effects.[47] A comprehensive meta-analysis of 11 RCTs including 569 overweight or obese participants confirmed significant reductions in body weight, BMI, and waist circumference, along with improved inflammatory and metabolic profiles (C-reactive protein (CRP), total cholesterol, homeostatic model assessment for insulin resistance (HOMA-IR)), though effects on WHR and total body fat were not significant. The overall evidence quality was rated as moderate to low due to small sample sizes, short follow-up, and parameter heterogeneity.[49]

Exercise-combined PBMT protocols have also demonstrated synergistic benefits. In a trial exploring the combined effects of LLLT and exercise, 36 women exhibited moderate improvements in lipolysis with LLLT combined with aerobic exercise, but no marked advantage over aerobic exercise alone.[56] A study involving 49 women with obesity aged 20–40 demonstrated that 808 nm infrared laser combined with aerobic and resistance training resulted in superior improvements in weight, fat mass, insulin resistance, and inflammatory markers compared to the control group.[57] A double-blind experiment with 64 women further confirmed that integrating LLLT with aerobic and resistance training significantly reduced cardiovascular metabolic risk, notably by lowering inflammatory markers and visceral fat.[35] However, some studies suggested limited efficacy in alleviating muscle fatigue among athletes engaged in high-intensity training.[48]

Retrospective analyses have provided further clinical validation. A 635 nm laser treatment of 86 patients resulted in significant reductions in waist-to-hip and thigh circumference with no adverse effects.[44] Another study involving 30

Table 2 Clinical Studies of Phototherapy

Therapy	Device/Method	Study Design	Efficacy	Satisfaction/Safety	Ref.
PTT	980, 1064, 1320 nm laser	Clinical trial	Reduced fat thickness, improved contour	Satisfaction >80%; mild adverse events	[12]
	1060 nm semiconductor laser	Multicenter clinical study	Reduced fat thickness	Satisfaction >90%; minimally invasive	[34]
	1064 nm laser + cooling system	Clinical trial (n=1)	Reduced abdominal fat thickness, reduced waist circumference	Safe and effective	[35]
	Long-pulse 1060 nm laser	Prospective clinical study (n=60)	Reduced subcutaneous fat thickness	Good safety profile	[36]
	755 nm picosecond laser + 1060 nm laser	Prospective trial (n=11)	Improved neck laxity	Safe and effective	[37]
	1064 nm Nd:YAG laser	Prospective trial (n=10)	Reduced flank fat, improved skin tightness	Satisfaction >90%	[38]
	Endolaser	JBI methodology for scoping reviews (26 studies included)	Improved facial contour, reduced fat, promoted skin rejuvenation	High satisfaction	[39]
PBM	630, 850 nm laser	RCT (n=90)	Reduced abdominal circumference	Satisfaction >90%	[40]
	635 nm laser	RCT (n=54)	Reduced subcutaneous fat thickness, improved waist-hip ratio	Safe and effective	[41]
	532 nm laser	RCT (n=60)	Reduced weight, BMI, waist circumference, body fat	Satisfaction >60%	[42]
	635 nm LLLT device	Review (7 studies included)	Reduced upper arm, waist, hip, and thigh circumference	High satisfaction; safe and effective	[43]
	Erchonia® Zerona Laser 635 nm	Retrospective clinical study (n=86)	Reduced total average circumference	Safe and effective	[44]
	Zerona™ multi-head diode laser device (635 nm)	Multicenter retrospective study (n=689)	Reduced waist, hip, thigh circumference	Safe and effective	[45]
	1060-nm diode laser + 635-nm LLLT	Prospective multicenter clinical trial (n=44)	Reduced subcutaneous fat thickness	Satisfaction 96%; safe and effective	[46]
	630, 808 nm laser + 450 nm blue LED	Pre-post self-controlled case series (n=18)	Reduced abdominal circumference	Safe and effective	[47]
	Multi-wavelength laser + LED	RCT (n=16)	No difference in post-exercise fatigue or muscle injury markers between PBMT and placebo	Safe but ineffective	[48]
	Low-level laser therapy device	RCT (11 studies included)	Reduced weight, BMI, waist circumference, CRP, total cholesterol	Safe and effective	[49]
	Antares® device	Non-randomized controlled study (n=10)	Increased expression of apoptosis markers	Safe	[50]
	Volcano device (532 nm green LED laser)	Retrospective study (n=30)	Reduced abdominal, thigh, and arm circumference	High satisfaction; safe and effective	[51]
	Lipo Laser 650 nm	Prospective self-controlled study (n=17)	No significant local fat reduction; overall weight and waist circumference reduced	4 cases with persistent erythema; 5 dropouts	[52]
	Erchonia EML Laser (Zerona™) 635 nm	Split RCT (n=5)	No clinical difference	Low satisfaction; safe	[53]
	810 nm LaserPen + acupuncture	RCT (n=62)	Reduced BMI and BFP	Safe and effective	[54]
	Laser Watch + low-calorie diet	RCT (n=60)	Reduced weight, BMI, and waist circumference	Safe and effective	[55]
	Abdominal low-level laser + exercise	RCT (n=36)	No efficacy observed	Safe	[56]
	Infrared laser device + exercise	RCT (n1=42; n2=64)	Reduced weight, BMI, body fat, visceral fat, waist circumference; decreased insulin and HOMA-IR	Safe and effective	[57,58]

women (BMI > 28) reported substantial decreases in body measurements following 532 nm green LED therapy, confirming its safety and high satisfaction.[51] A large-scale retrospective series of 689 subjects treated with LLLT achieved an average total circumference reduction of 3.27 inches without serious adverse effects.[45] Conversely, isolated reports indicated inconsistent results: a 2017 controlled study observed minimal fat reduction with some side effects,[52] and a small double-blind trial involving five participants found no significant improvement and low satisfaction.[53]

Collectively, PBMT demonstrates consistent efficacy in reducing localized fat and improving metabolic parameters with a high safety profile. However, variations in wavelength, energy dose, and treatment frequency contribute to heterogeneity across studies. Further well-designed RCTs with standardized protocols and long-term follow-up are needed to establish optimal parameters and mechanisms of action.

Mechanisms of Phototherapy in Non-Invasive Lipolysis

Inhibiting angiogenesis in WAT and promoting its conversion to brown adipose tissue (BAT) are pivotal strategies for reducing adiposity. Angiogenesis in WAT is closely linked to adipocyte development, and by disrupting the blood supply in WAT, adipocyte growth is inhibited, fat tissue is reduced, and body weight is lowered. By delivering pro-apoptotic peptides to WAT using the marker Prohibitin (PHB), endothelial cell apoptosis can be induced, reducing blood supply and decreasing WAT volume.[14] Mouse studies have demonstrated that employing nanotechnology and molecules such as RSG, Dibenzazepine, and Resveratrol to activate signaling pathways like peroxisome proliferators-activated receptor gamma (PPARγ), Notch, and Sirtuin can promote the conversion of WAT to BAT. Additionally, LED light exposure and temperature elevation further enhance adipocyte thermogenesis and metabolism by increasing UCP1 expression and activating Transient Receptor Potential Vanilloid 1 (TRPV1), supporting adipose browning and energy expenditure[14] (Table 3 and Figure 2).

Photodynamic Therapy

PDT employs photosensitizers to generate ROS under specific light conditions, specifically targeting adipocyte membranes or particular cells to achieve fat degradation, metabolic modulation, and therapeutic enhancement.

ROS Generation and Controlled Adipocyte Apoptosis

Phototherapy induces ROS production, which plays a pivotal role in adipocyte apoptosis and metabolic regulation. Under LED irradiation, photosensitizers such as chlorin e6 (Ce6) generate singlet oxygen and other ROS, transiently disrupting the adipocyte membrane and releasing intracellular contents, followed by membrane self-repair. This controlled membrane damage facilitates gradual adipocyte apoptosis, effectively reducing lipid accumulation.[59] Building on this concept, recent studies have developed cold atmospheric plasma (CAP)-responsive nanoparticles (RANP) that amplify intracellular ROS for obesity therapy. RANP encapsulates LDH and NADH within lipid nanoparticles, establishing an enzymatic ROS cycle upon CAP stimulation, overcoming CAP's limited tissue penetration and ROS short half-life. In vitro, RANP + CAP decreases adipocyte viability, reduces lipid droplet size, induces apoptosis, and upregulates UCP1 to promote browning. In vivo, high-fat diet mice treated with RANP + CAP show significant reductions in body weight, subcutaneous and visceral fat volumes, and hepatic TG, along with enhanced thermogenesis. These findings demonstrate that ROS amplification strategies can achieve effective, localized lipolysis and metabolic improvement.[33]

Lipid Peroxidation and Cell Apoptosis

Aggregation-induced emissive luminogens (AIEgens), specifically TTMN and MeTTMN, generate a substantial amount of ROS upon light exposure, triggering lipid peroxidation similar to ferroptosis, ultimately leading to adipocyte apoptosis. Due to their unique AIE properties, these photosensitizers efficiently accumulate in lipid droplets, enhancing ROS generation. MeTTMN can persistently generate ROS in hypoxic environments, overcoming the limitations of traditional photosensitizers that perform poorly under low-oxygen conditions. This renders PDT suitable for treating tumors and other hypoxic environments, thereby expanding its therapeutic applications.[15]

Table 3 Molecular Mechanisms and Biological Therapeutic Effects of Phototherapy for Fat Reduction

Method/Material	Main Mechanism	Experimental/Clinical Findings	Applications/Prospects	Ref.
PDT				
Ce6-PDT	Ce6 activated by 660 nm light produces ROS, disrupting adipocyte membranes and activating AMPK while suppressing SREBP-1c and inflammatory cytokines	Significant reduction in body weight and fat mass; improved liver function and lipid profile	Non-invasive therapy for obesity and non-alcoholic fatty liver disease (NAFLD)	[59]
AIE photosensitizer (TTMN/MeTTMN) + white light	Hydroxyl radicals and superoxide induce lipid peroxidation, triggering ferroptosis-like adipocyte death	Adipocyte viability decreased by >70%; significant reduction in body weight and adipose tissue in mice	Targeted photodynamic fat reduction	[15]
Ce6-PDT + OA targeting GPR119 receptor	Photoinduced ROS leads to K-cell apoptosis and reduced GIP secretion	80% decrease in body weight, 47% reduction in fat mass, improved glycemic control	Endoscopic PDT for obesity and type 2 diabetes mellitus (T2DM)	[16]
Pep-PPIX-Baic ultrasmall hybrid nanoparticles	Photoactivation generates ROS, activating the p-AMPK/PGC-1α/UCP1 pathway and promoting white-to-brown fat conversion.	Induced adipocyte death and browning, enhanced energy expenditure, and exhibited high biosafety.	Non-invasive photodynamic fat reduction.	[22]
CAP-responsive nanoparticles	CAP stimulation initiates the LDH/NADH enzymatic redox cycle, amplifying ROS and activating UCP1/HIF-1α/iNOS to promote lipolysis and browning.	Enhanced lipolysis, apoptosis, and browning; reduced fat and hepatic steatosis.	Non-invasive nano–plasma-assisted fat reduction.	[33]
PTT				
CuS-NDs (NIR-II, 1064 nm)	Heat activates TRPV1 channels → Ca^{2}+ influx → upregulation of PPARγ/UCP1 → adipose browning and lipolysis	15% body weight loss, 40–54% fat reduction, improved glucose and insulin sensitivity	Minimally invasive photothermal–metabolic combined therapy	[18]
Long-pulse 1060 nm laser (45 °C, 15 min)	Thermal damage activates ALOX15–p38 MAPK signaling, promoting ECM protein synthesis	Decreased fat thickness, skin tightening, no significant change in blood lipids	Non-invasive body contouring and skin tightening	[36]
PAAu BPs nanosheets (808 nm)	PS signal recruits macrophages to clear adipocytes and induces lipolysis via photothermal effects	24–33% weight loss, fat reduction, metabolic improvement	Immuno-photothermal anti-obesity therapy	[60]
AHP-KLA liposomes/AuNPs	Targeting prohibitin receptor; KLA peptide induces mitochondrial apoptosis and inhibits adipose angiogenesis	Significant reductions in weight and fat mass; improved metabolic function	Anti-angiogenic photothermal therapy for obesity	[14]
DBZ/Res/Rosi nanoparticles (microneedle patch)	Notch inhibition + Sirtuin/PPARγ activation → conversion of white to brown adipose tissue	Induced browning, reduced body weight, improved lipid profile	Browning-induced metabolic therapy	[14]
Gold nanoparticles (AuNPs/AuNRs)	Localized surface plasmon resonance-induced heating causes adipocyte necrosis and lipolysis	Local fat reduction confirmed in animals and early human trials	Minimally invasive localized lipolysis	[14]
GG–melanoidin photothermal agent	Absorption at 808 nm generates heat → adipocyte membrane rupture and lipid release	Significant adipose tissue reduction in mice; H&E staining confirmed cell destruction	Non-invasive fat ablation	[61]
pTSL@(P+I)	Combined photothermal and pharmacological upregulation of UCP1/COX5B promotes browning and lipolysis	14% weight reduction, smaller adipocytes, improved lipid profile	Targeted photothermal–pharmacologic therapy	[2]
HA–HAuNS–ATP composite	HA enhances transdermal delivery; gold nanospheres generate heat leading to adipocyte necrosis	Decreased PA signal in adipose tissue	Transdermal non-invasive fat lysis	[1]
BP–PolyMet–P3–HA composite	BP photothermal heating + AMPK activation + anti-inflammatory effects → UCP1 upregulation	Reduced weight and fat mass, enhanced insulin sensitivity	Targeted multifunctional anti-obesity photothermal therapy	[62]
SDAR photothermal hydrogel (with resveratrol nanoparticles)	Photothermal heating synergizes with resveratrol to modulate ROS, PPARγ, C/EBPα, and UCP1, suppressing adipogenesis and enhancing browning.	Reduced adipogenesis and inflammation, upregulated UCP1, antioxidant and anti-inflammatory effects.	Synergistic photothermal–pharmacologic anti-adipogenic therapy.	[17]
PBNP@SF + 808 nm NIR	Photothermal activation triggers TRPV1/HSF1–PGC1α–UCP1 axis and ROS signaling, promoting browning and lipid droplet degradation.	9.78% weight loss; 53.95% reduction in subcutaneous fat, 65.37% in visceral fat; high biosafety.	Photothermal–nanocatalytic combined fat reduction.	[28]
Chitosan nanoparticles + ICG foaming microneedle	Photothermal stimulation induces autophagy via LC3-II/autophagy–lysosome/UCP1 signaling, promoting lipid degradation and browning.	Induced lipophagy and browning; 38% weight loss; improved metabolic function.	Photothermal microneedle–nanoparticle autophagy-mediated lipolysis.	[31]
Soy lecithin–polypyrrole "pufferfish-like" nanoparticles	Photothermal heating activates UCP1/TRPV1/Ahr pathways and inhibits PPARγ, inducing browning and apoptosis.	Induced adipocyte browning and apoptosis; reduced weight and lipid levels; strong adipose targeting.	Targeted photothermal fat reduction.	[30]
AuNR–PPARγ antibody complex	Photothermal effect activates PPARγ–Bax–Caspase-3 signaling, inducing apoptosis.	Specific adipocyte apoptosis; significantly reduced fat thickness; high safety profile.	Minimally invasive targeted local fat reduction.	[29]

(*Continued*)

Table 3 (Continued).

Method/Material	Main Mechanism	Experimental/Clinical Findings	Applications/Prospects	Ref.
Rosiglitazone-loaded cationic albumin nanoparticles + IR780 thermosensitive hydrogel	Photothermal stimulation activates TRPV1/AMPK/PGC1α, while rosiglitazone activates PPARγ/UCP1, synergistically enhancing browning and energy metabolism.	Promoted browning and energy expenditure; reduced weight and lipids; improved metabolic disorders and hepatic steatosis.	Photothermal–pharmacologic synergistic adipose-targeted therapy.	[32]
PBM				
PBM (red/NIR 630–850 nm)	Light absorbed by cytochrome c oxidase ↑ATP, ROS, NO, and cAMP → activates lipolysis and transient membrane pores for triglyceride release	Significant waist and local fat reduction; improved cholesterol, TG, and cellulite appearance	Non-invasive body contouring and lipolysis adjunct	[63–65]
PBM (red 660 nm + NIR 850 nm)	Activates caspase-3 and autophagic lipolysis; induces adipocyte apoptosis and macrophage clearance	Fat layer thinning and adipocyte degeneration without adverse effects	Non-invasive body remodeling and lipolytic enhancement	[50]
PBMT (635 nm)	↑ROS → inhibits PTEN → activates AKT–FoxO1 pathway → downregulates ATGL to suppress lipolysis	Decreased FFA/TG; improved glucose tolerance and insulin sensitivity	Novel physical therapy for type 2 diabetes and insulin resistance	[26]
PBM systemic metabolic modulation hypothesis	PBM may modulate systemic lipid metabolism rather than induce local tissue damage	Local fat thickness change not significant ($p = 0.47$); minor adverse events (4/24); some increase observed	Suggests PBM acts systemically; effective when combined with exercise	[52]
PBM + aerobic/resistance exercise	PBM-induced ROS and cAMP promote lipolysis; exercise enhances β-adrenergic-mediated lipolysis and energy utilization	Increased glycerol, enhanced lipolysis; reduced body fat %, waist circumference, HOMA-IR, and leptin	Non-invasive combined therapy for metabolic syndrome and obesity	[37,58]
PBM + low-calorie diet (LCD)	Activates cAMP pathway, improves insulin sensitivity, suppresses inflammatory mediators	13% weight loss, BMI − 11 kg/m^2, reduced inflammation and depression indices	Comprehensive intervention for menopausal and metabolic syndrome females	[55,66]
Multi-wavelength PBM (red/infrared/blue + medium-frequency current)	Multi-spectral stimulation of mitochondrial and hemoglobin complexes enhances lipolysis, circulation, and oxidation	Average waist reduction 4–5 cm ($p < 0.001$); improved local circulation and self-esteem	Multi-wavelength non-invasive body contouring and metabolic health enhancement	[47,67–69]

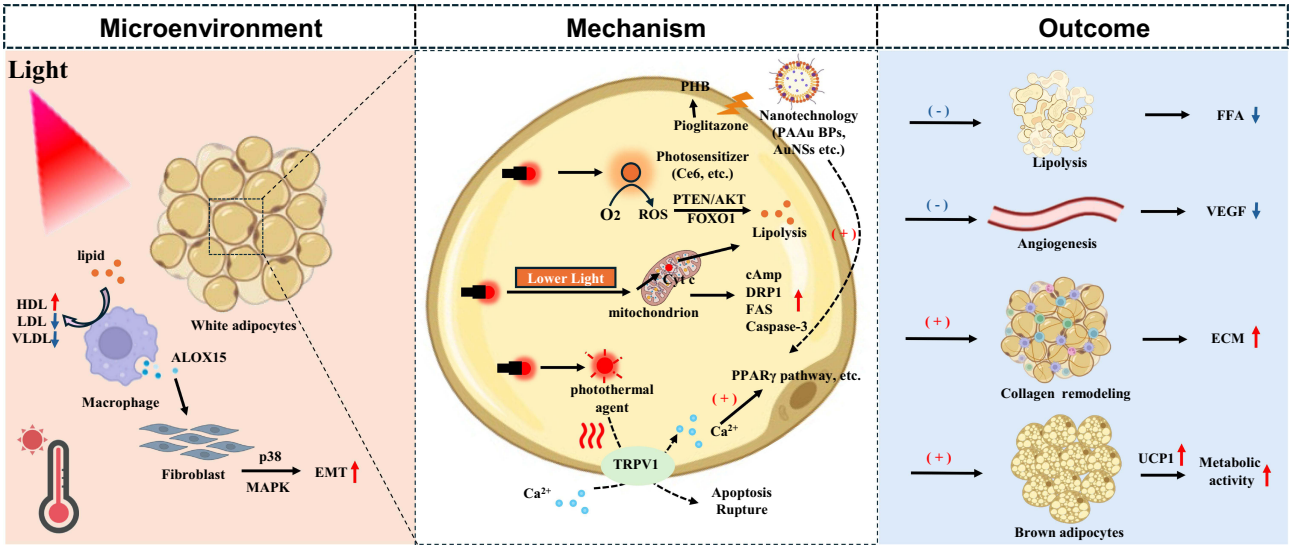

Figure 2 Mechanisms of phototherapy in fat breakdown and conversion. ↑, increase; ↓, decrease; (+), promotion; (-), inhibition.

Synergistic PDT and Browning Induction

Recent work (Small, 2023) developed Pep-PPIX-Baic NPs that combine PDT with browning induction for obesity treatment. The nanoparticles contain a targeting peptide (CKGGRAKDC) for adipose tissue, PPIX generating ROS under laser, Fe^{3}+ to enhance PDT, and baicalin to induce white-to-brown fat conversion. Self-assembled ~6.5 nm particles exhibit good stability, biocompatibility, and adipocyte uptake. In vitro, they produce ROS efficiently, induce adipocyte apoptosis, upregulate thermogenic and mitochondrial genes (UCP1, PGC-1α, beta-3 adrenergic receptor (ADRB3), mitochondrial transcription factor A (TFAM), cytochrome c oxidase subunit (COX) 8B, cytochrome c oxidase subunit 7A1), and activate the phosphorylated AMP-activated protein kinase (p-AMPK) pathway. In vivo, laser-irradiated particles reduce body weight and white fat, increase brown fat, elevate UCP1, enhance thermogenesis, and improve metabolic profiles (total cholesterol, high-density lipoprotein cholesterol (HDL-C)) without affecting food intake. No obvious toxicity was observed. This strategy highlights the potential of combining PDT with browning induction for efficient, safe, and targeted anti-obesity therapy.[22]

Targeted Delivery and Metabolic Improvement

OPC specifically targets K cells via binding to the G protein-coupled receptor (GPR 119) receptor, generating ROS under laser exposure, and selectively inducing K cell apoptosis while reducing GIP secretion. This targeted mechanism spares other intestinal cells, minimizing side effects, and by inhibiting GIP, effectively enhancing glucose metabolism, demonstrating significant anti-obesity and anti-diabetic effects.[16] This strategy is effective not only for fat reduction but also in regulating systemic metabolism, offering an innovative solution for the application of PDT in metabolic diseases such as obesity and type 2 diabetes.[16]

Photothermal Therapy

Photothermal lipolysis achieves fat cell browning, lipolysis, and metabolic improvement by inducing temperature-dependent molecular pathways and selectively damaging adipocytes. Combined with synergistic drug delivery and targeted nanomaterial design, PTT offers efficient and safe fat reduction while improving lipid metabolism, presenting an innovative approach for body contouring and fat reduction.

Temperature-Induced Adipocyte Damage and Apoptosis

Laser lipolysis employs the photothermal effect to rupture adipocyte membranes, releasing fat contents, which are then drained through the lymphatic system. The heat from the laser also affects collagen fibers in the subcutaneous tissue,

promoting their thermal contraction and remodeling, resulting in skin tightening. Neodymium-doped Yttrium Aluminum Garnet (Nd:YAG) 1064 nm laser effectively coagulates blood vessels, reducing bleeding, bruising, and post-operative swelling. However, the lipolysis effect depends on the laser energy level; higher energy results in more significant fat breakdown but also raises the risk of tissue damage.[12,23] To prevent epidermal damage, an air cooling system maintains a lower surface temperature, facilitating deeper heat accumulation for effective fat dissolution while minimizing the risk of skin burns.[35] To overcome the challenge of limited light penetration in tissues, researchers have developed microneedle designs that deliver light energy directly to deeper layers. These novel optical fiber microneedles are capable of evenly transmitting light energy, significantly reducing localized overheating and carbonization effects.[70]

Transient Receptor Potential Vanilloid 1 Activation and Adipocyte Browning

Elevated temperature triggers TRPV1 channels on adipocyte membranes, allowing calcium ions to flow in and activate the PPARγ pathway, which promotes adipocyte browning, enhances UCP1 protein expression, and boosts metabolic activity. This process is a key feature of PTT, significantly accelerating fat degradation. Temperature also activates adipocyte enzymes such as hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), breaking down lipid droplets and releasing FFAs, further promoting lipolysis. Moreover, when used in conjunction with drugs such as mirabegron, PTT has the potential to activate β3 adrenergic receptors (β3AR), enhancing adipocyte browning and lipolysis, improving insulin sensitivity, and increasing adiponectin secretion, thereby optimizing systemic metabolism.[18] Recent mechanistic studies have revealed that Prussian blue nanoparticle–based silk fibroin hydrogels (mPTT-NCT) integrate TRPV1 activation with the heat shock factor 1 (HSF1)– heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1)–PGC1α–UCP1 axis, stabilizing thermogenic gene expression while mimicking antioxidant enzyme activity (superoxide dismutase/catalase, SOD/CAT) to scavenge ROS and reduce inflammation. This dual photothermal–nanocatalytic system simultaneously enhances thermogenesis and metabolic homeostasis in obese models.[28]

Immune System Clearance and Metabolic Improvement

Photothermal therapy-induced adipocyte necrosis triggers a localized inflammatory response, where immune cells, such as macrophages, clear the remnants of dead fat cells.[23] Within 14 days, necrotic adipocytes are replaced by fibrous tissue, reducing fat thickness and reshaping the body. Laser treatment at 45°C causes thermal damage to adipocytes, releasing lipids that are engulfed by macrophages, increasing high-density lipoprotein (HDL) levels and lowering low-density lipoprotein (LDL) and very low-density lipoprotein cholesterol (VLDL), promoting lipid transport and metabolic improvement.[18] Additionally, activation of Arachidonate 15-Lipoxygenase (ALOX15) generates 12(S)-hydroxyeicosatetraenoic acid (12(S)-HETE), activating the p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway in fibroblasts, stimulating extracellular matrix protein production, including collagen I and fibronectin.[36]

Gold nanoparticle bipyramids (PAAu BPs), modified to resemble apoptotic cells, specifically target adipocytes. When exposed to external infrared laser irradiation, PAAu BPs generate a photothermal effect that disrupts adipocyte structures and promotes fat degradation. The exposure of phosphatidylserine (PS) on PAAu BPs mimics apoptotic signaling, attracting macrophages for clearance. This immune process reduces adipocyte numbers, with macrophages shifting from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype, improving the adipose tissue microenvironment and reducing inflammation. The photothermal effect further enhances fat breakdown, improving fat loss outcomes.[60]

Targeting of Nanomaterials and Photothermal Conversion Efficiency

Temperature-sensitive nanoparticles, such as PAAu-BP and glycol-glycerol-melanin (GG-melanin), generate localized heat through efficient photothermal conversion in adipose tissue, thereby inducing lipolysis and immune clearance. The core mechanism involves absorption of NIR light and conversion to thermal energy, causing increased membrane permeability, mitochondrial dysfunction, and lipid droplet degradation. Gold nanospheres (AuNS) and AuNR exploit surface plasmon resonance for precise infrared absorption under 808 nm irradiation, triggering apoptotic signaling (Bcl-2-associated X protein (Bax)/Caspase-3 upregulation) in adipocytes for selective fat ablation while sparing surrounding tissues.[14] GG-melanin synthesized via the Maillard reaction exhibits strong NIR absorption and electron transfer capability; coordination with iron ions enhances photothermal efficiency, stabilizes local temperature, upregulates thermogenic markers (UCP1, COX5B), and its renal excretion reduces long-term toxicity.[61]

In a study, temperature-sensitive liposomes (pTSLs) were modified with a fat-targeting peptide (CKGGRAKDC sequence) and loaded with Pioglitazone and IR780. Upon activation by 808 nm NIR light, the complex generates heat, promoting adipocyte browning and fat reduction. The complex targets PHB protein on adipocyte surfaces, utilizing the synergy of photothermal therapy and drug delivery to enhance fat browning and energy expenditure. IR780-induced heat activates the HSF1 /PGC1α axis, further inducing expression of UCP1 and COX5B, while Pioglitazone promotes fat browning through the PPARγ/PGC1α pathway, enhancing therapeutic efficiency and stability.[2] A novel nanocarrier was developed by combining hyaluronic acid (HA) with hollow gold nanospheres (HAuNS), leveraging the skin-penetrating properties of HA for non-invasive delivery, while enhancing fat tissue targeting through adipocyte-targeting peptides (ATP). Upon NIR light exposure, this nanocomplex generates localized heat that induces adipocyte damage and apoptosis, with necrotic cells being cleared by the immune system, ultimately reducing fat accumulation.[1]

Using electrostatic layer-by-layer self-assembly, researchers constructed a P3-HA/PM@BP "nanocapsule" material, in which PolyMet inhibits lipogenesis and reduces inflammation via activation of the AMPK pathway, while black phosphorus nanosheets (BP) triggers adipocyte apoptosis and lipolysis through the photothermal effect. HA and P3 provide targeted functions, facilitating the nanocarrier's targeted accumulation in adipose tissue. This dual-targeted design, through the synergistic effects of AMPK activation and PTT, significantly improves adipocyte lipolysis efficiency, inhibits fat formation, and promotes enhanced fat metabolism.[62]

Recently, photothermal lipolysis strategies have evolved from simple thermal ablation to multidimensional photothermal-molecular regulation paradigms. The core mechanism integrates local photothermal stimulation with adipose metabolism, inflammation modulation, autophagy, and browning pathways, achieving efficient and safe adipocyte ablation and metabolic remodeling. Photothermal-responsive alginate hydrogel loaded with SDAR maintains ~44°C under NIR irradiation, inducing mild hyperthermia that increases adipocyte membrane permeability and remodels lipid droplets. Resveratrol simultaneously downregulates adipogenic transcription factors PPARγ and CCAAT/enhancer-binding protein alpha (C/EBPα), upregulates thermogenic protein UCP1, and activates hypoxia-inducible factor 1 (HIF-1) and phosphoinositide 3-kinase-Protein kinase B (PI3K-Akt) pathways, suppressing adipogenesis while enhancing thermogenesis. This approach integrates photothermal energy conversion with metabolic and inflammatory modulation, offering a safe and efficient non-invasive strategy for obesity management.[17] In addition, EMN systems co-deliver stearic acid-modified chitosan nanoparticles (COA NPs) and ICG via CO_2 effervescence for rapid transdermal penetration and sustained intradermal release. ICG under NIR irradiation induces mild hyperthermia, activating UCP1 to drive adipocyte browning, while COA NPs target adipocytes electrostatically and trigger autophagy-lysosomal degradation of lipid droplets (upregulating microtubule-associated proteins 1A/1B light chain 3B-II (LC3-II)). Combined treatment significantly reduces subcutaneous and visceral fat in diet-induced obese mice, improves glucose tolerance and lipid profiles without systemic toxicity, demonstrating a photothermal-autophagy-metabolism triple synergistic mechanism.[31] Meanwhile, microwave-synthesized lecithin-polypyrrole "nano-pufferfish" particles (MSL-PPy NPs) accumulate precisely in adipose tissue via lipid affinity and rapidly elevate local temperature to ~58°C under 808 nm irradiation, inducing adipocyte apoptosis and browning-like morphological changes. Mechanistically, MSL-PPy NPs combined with photothermal treatment upregulate UCP1 and TRPV1, activate the aryl hydrocarbon receptor (Ahr) pathway, and destabilize PPARγ to suppress adipogenesis, remodeling adipose energy metabolism. Compared to microneedle systems, this platform achieves adipose-selective photothermal modulation without external carriers, representing another efficient non-invasive mechanism.[30] Zhang et al developed cationic albumin nanoparticles (cNPs) loaded with RSG, combined with thermosensitive hydrogel (F127) and photothermal agent IR780, achieving adipocyte-targeted delivery and local photothermal therapy. Under NIR irradiation, IR780 generates mild hyperthermia activating TRPV1-Ca^{2}+ influx-AMPK/PGC1α pathway, while RSG activates PPARγ signaling, synergistically upregulating UCP1. This induces white fat browning, lipid droplet degradation, and lipid consumption. In vivo, the cNPs + PTT group significantly reduced body weight, subcutaneous and visceral fat, improved glucose tolerance and lipid profiles, decreased hepatic lipid deposition, and showed no organ toxicity, demonstrating a dual mechanism of charge-mediated adipocyte targeting and heat-induced browning.[32] Moreover, Gold-based nanomaterials conjugated with adipocyte-specific antibodies selectively accumulate in adipocytes under NIR irradiation, inducing controlled adipocyte apoptosis via mitochondrial pathways (Bax/

Caspase-3 upregulation, TUNEL positive). Animal studies show significant reduction in local fat thickness without affecting surrounding tissues. Overall, nanophotothermal systems integrate targeted delivery, mild heating, and signaling pathway modulation to achieve precise adipocyte apoptosis, lipid clearance, and white fat browning, providing a translatable framework for non-invasive photothermal lipolysis.[29]

Photobiomodulation

PBMT stimulates mitochondrial activity and signaling pathways to enhance lipolysis, improve metabolism, reduce inflammation, and significantly decrease fat volume. Its main mechanisms include enhancing cellular energy metabolism, promoting lipid efflux, inhibiting fat accumulation, and enhancing insulin sensitivity while exerting anti-inflammatory effects.

PBMT creates micropores in the adipocyte membrane, promoting lipid efflux, thereby facilitating metabolic clearance from the cell.[47] This lipid transfer mechanism operates independently of complement activation. Some studies have observed an increase in fat thickness in certain patients, which cannot be entirely accounted for by traditional membrane disruption models.[56,63] Researchers hypothesize that LLLT operates through the regulation of systemic lipid metabolism, rather than purely local cell damage.[52] Additionally, PBMT induces adipocyte apoptosis by increasing the expression of Caspase 3 and Cleaved Caspase 3, resulting in sustained reductions in fat volume.[50]

Studies demonstrate that PBMT significantly promotes lipolysis and enhances metabolic function through multiple mechanisms. Initially, PBMT penetrates the skin using red and infrared light, activating cytochrome c oxidase in the mitochondria, which increases ATP synthesis and enhances cellular metabolism. This process activates the cyclic adenosine monophosphate (cAMP) pathway, thereby facilitating the release of fatty acids and glycerol, thereby supporting fat breakdown.[55,56] PBMT also induces the generation of ROS, which further enhances lipolysis and fatty acid release. ROS production inhibits phosphatase and tensin homologue (PTEN), activates the protein kinase B (AKT) pathway, and suppresses Forkhead box transcription factor O1 (FoxO1) transcription, thereby decreasing ATGL expression in adipocytes, limiting triglyceride hydrolysis, and reducing free fatty acid release. Through activation of the PTEN/AKT/FoxO1 pathway, PBMT effectively suppresses lipolysis under insulin resistance conditions, thereby improving overall insulin sensitivity.[26] Furthermore, PBMT enhances mitochondrial function, reduces the accumulation of fatty acid metabolites, and inhibits the stress kinase c-Jun NH2-terminal kinase (JNK), thereby improving insulin signaling. Research indicates that PBMT activates key signaling molecules, including Akt and Akt substrate of 160 kDa (AS160) phosphorylation, and promotes glucose transporter type 4 (GLUT4) translocation, thereby enhancing glucose uptake by cells.[66] Other research suggests that low-intensity laser (Laser biostimulation) therapy enhances insulin sensitivity, potentially through its effects on reducing inflammation and regulating the potassium-sodium ion balance in the cell membrane, which helps alleviate insulin resistance and reduce the risk of metabolic syndrome.[55] Additionally, PBMT helps reduce oxidative stress in adipocytes, thereby decreasing lipid accumulation and enhancing lipid metabolism.[70]

PBMT exhibits substantial anti-inflammatory effects by reducing the production of pro-inflammatory cytokines, modulating immune responses, and enhancing tissue repair, particularly in muscle and nerve tissues.[55,67] Research indicates that PBMT alleviates tissue inflammation through increased nitric oxide (NO) release and regulation of calcium ion channels, while also altering macrophage phenotype from pro-inflammatory M1 to anti-inflammatory M2. This mechanism promotes fat metabolism and reduces systemic inflammation.[68,69] Furthermore, PBMT improves local blood circulation and oxygenation through blue light-induced NO release, supporting lipolysis and the clearance of metabolic waste.[47] LLLT also enhances mitochondrial membrane potential in both adipocytes and muscle tissue, increasing ATP production and accelerating the release of fatty acids and glycerol. The laser further activates HSL, promoting lipolysis and reducing pro-inflammatory factors such as leptin and intracellular adhesion molecule 1 (ICAM-1), effectively mitigating obesity-induced systemic inflammation.[58] In addition, LLLT induces a hypoxic environment in skin tissue, which helps maintain a stable anti-inflammatory microenvironment, a mechanism particularly beneficial for wound healing and treating inflammatory conditions such as acne.[71]

Challenges and Future Prospects of Phototherapy

Personalized treatments, combination therapies, and the use of light-sensitive materials have shown significant potential in obesity management and body contouring, advancing non-invasive techniques. These strategies enhance efficacy, minimize side effects, and offer safer, more sustainable options. Phototherapy aids fat metabolism and metabolic improvements through various biological pathways, though the exact mechanisms are not fully understood. Research indicates that phototherapy generates ROS via photosensitizers, activating cellular signaling pathways like AKT, cAMP and PPARγ, promoting lipolysis, improving insulin sensitivity, and reducing fat accumulation. However, the interactions between these mechanisms and their effects on different adipocyte types remain unclear. Additionally, factors such as light source, wavelength, energy intensity, and exposure methods may influence pathway activation, complicating the understanding of these processes.

Individual variations in fat distribution and metabolism affect treatment outcomes; thus, personalized approaches should incorporate genomic and biomarker profiling to optimize parameters such as wavelength, light intensity, and treatment frequency. For severe obesity or specific contouring needs, combination therapies such as PDT or PTT can target deeper adipose layers to enhance lipolytic efficacy. Integrating PBMT with aerobic exercise has also been shown to promote fat breakdown and improve metabolic health.[14,23,24,27]

Individual variations in fat distribution and metabolism affect outcomes, and personalized treatments should incorporate genomics and biomarkers to tailor interventions, adjusting factors like light intensity and frequency. For severe obesity or specific body contouring needs, combination therapies like PDT or PTT can target deeper fat layers, improving treatment efficacy. Combining PBMT with aerobic exercise enhances fat breakdown and metabolic health.[14,23,24,27]

Emerging Potential of Nanotechnology in Phototherapy

The rapid advancement of nanotechnology has further expanded the therapeutic frontier of phototherapy. Although current clinical trials on PTT, PDT, and PBMT have primarily utilized traditional laser and LED systems without nanomaterial involvement, preclinical research demonstrates that nanostructures can markedly enhance phototherapeutic precision and efficiency. As carriers for photosensitizers or photothermal agents, nanomaterials—such as AuNR, carbon-based nanoparticles, and melanin-like polymers—can improve light energy absorption, tissue penetration, and selective accumulation in adipose tissue. These advantages facilitate more localized adipocyte apoptosis, adipose browning, and improved metabolic regulation.

In oncology,[72–74] nanomaterial-assisted PDT has already achieved superior efficacy through enhanced photosensitizer stability, targeting specificity, and photothermal conversion efficiency.[75–77] The underlying mechanisms, including ROS-mediated cell death, vascular remodeling, and metabolic modulation, are conceptually similar to the biological responses of adipose tissue under light exposure, providing a theoretical basis for extending such strategies to non-invasive lipolysis and metabolic regulation. Additionally, studies indicate that AuNPs in obesity-associated tumor microenvironments can improve lipid metabolism and alleviate inflammation, while providing targeting and ROS-generating capabilities.[78] This suggests that AuNPs or similar nanomaterials may synergistically enhance phototherapy-based obesity management by modulating adipose tissue metabolism, inflammation, and energy balance, thereby improving the precision and safety of photothermal or photodynamic interventions. Future nanomaterial-based PTT and PDT are expected to achieve deeper and more selective adipocyte ablation while minimizing collateral tissue damage. Notably, endogenous-like nanomaterials such as melanin,[61] owing to their strong light absorption and energy conversion efficiency, may further enhance phototherapy selectivity and safety. These innovations could pave the way for precision phototherapy in obesity management, offering novel avenues for improving insulin sensitivity, reducing lipid accumulation, and alleviating systemic inflammation[23,27,79] (Figure 3).

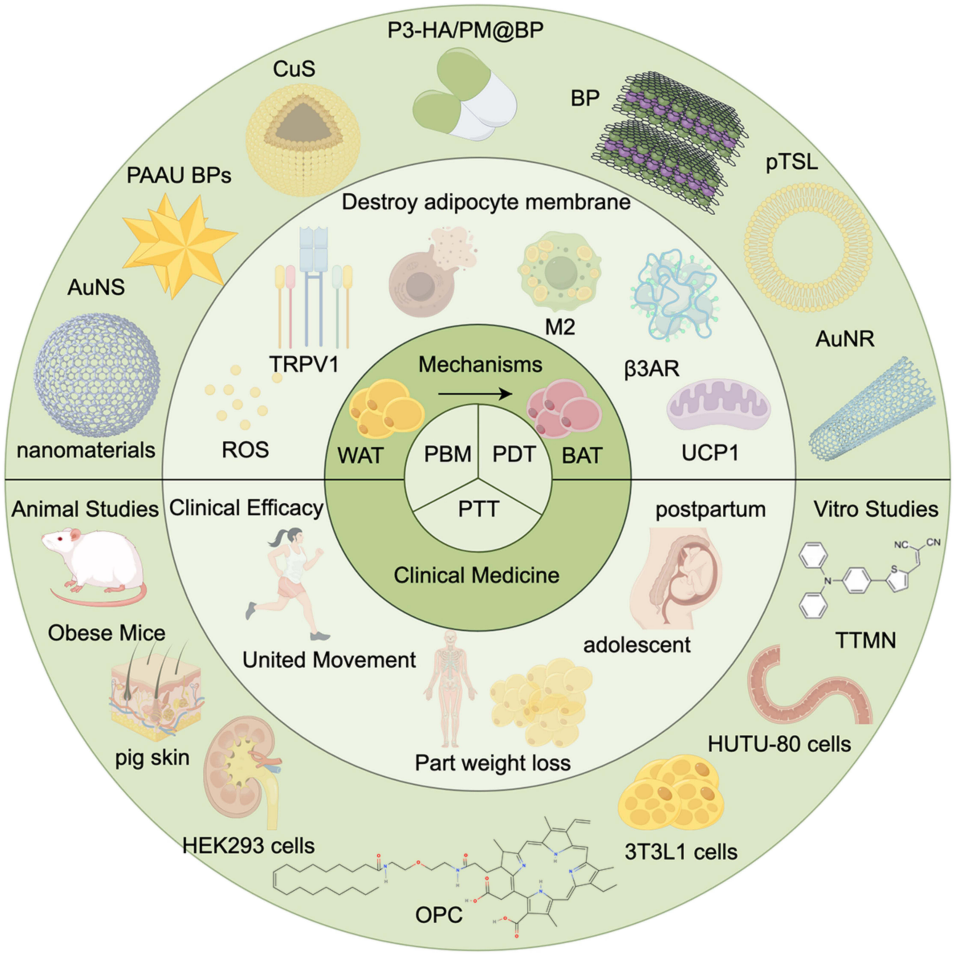

Figure 3 Phototherapy (PBMT, PDT, PTT) reduces fat non-invasively by modulating ROS, TRPV1, β3AR, and UCP1, with light-responsive nanomaterials like AuNS, CuS, and BP enhancing treatment precision. By Figdraw.

Conclusion

Non-invasive phototherapy holds great potential in obesity management, offering new avenues for safe and effective fat reduction. PDT, PTT, and PBMT improve body shape and contour by targeting adipose tissue, inducing adipocyte apoptosis, and enhancing lipid metabolism. The incorporation of nanomaterials markedly enhances the targeting and therapeutic efficacy of phototherapy, improving light delivery efficiency, precisely modulating ROS generation, and minimizing damage to surrounding tissues for safer and more efficient fat decomposition. Future studies should focus on the synergistic effects of nanomaterials and phototherapy, including the development of functionalized nanocarriers, optimization of optical parameters, and integration with other intervention strategies to achieve personalized and precise obesity management. The continued integration of nanotechnology is expected to provide new opportunities for the clinical translation of non-invasive fat reduction and drive innovative advances in obesity treatment.

Abbreviations

LLLT, low-level laser therapy; LAL, Laser-assisted lipolysis; PTT, photothermal therapy; PDT, photodynamic therapy; PBMT, photobiomodulation therapy; TTMN, Tetraphenylethene tetramethylthienothiophene-2-one; MeTTMN, Methylated tetraphenylethene tetramethylthienothiophene-2-one; ROS, reactive oxygen species; OPC, OA-PEG-Ce6, Oleic acid-poly (ethylene glycol)-chlorin e6; SDAR, resveratrol nanoparticle-loaded photothermal-responsive alginate hydrogel; NIR, near-infrared; FFA, free fatty acids; TUNEL, transferase-mediated dideoxyuridine triphosphate-biotin

nick end labeling; UCP1, uncoupling protein 1; PGC1α, proliferator-activated receptor gamma coactivator-1 alpha; WAT, white adipose tissue; OCT, Optical Coherence Tomography; ICG, Indocyanine Green; MB, methylene blue; GIP, gastric inhibitory polypeptide; Pep-PPIX-Baic NPs, ultra-small hybrid nanoparticle platform; PPIX, photosensitizer protoporphyrin IX; BG, brilliant green; LED, light-emitting diode; TG, triglycerides; PBNPs, Prussian blue nanoparticles; RCT, randomized controlled trial; NcRF, non-contact radiofrequency; BMI, body mass index; BFP, body fat percentage; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment for insulin resistance; BAT, brown adipose tissue; PHB, Prohibitin; PPARγ, peroxisome proliferators-activated receptor gamma; TRPV1, Transient Receptor Potential Vanilloid 1; CAP, cold atmospheric plasma; RANP, responsive nanoparticles; AIEgens, Aggregation-induced emissive luminogens; ADRB3, beta-3 adrenergic receptor; TFAM, mitochondrial transcription factor A; COX, cytochrome c oxidase subunit; p-AMPK, phosphorylated AMP-activated protein kinase; HDL-C, high-density lipoprotein cholesterol; GPR119, G protein-coupled receptor; Nd:YAG, Neodymium-doped Yttrium Aluminum Garnet; HSL, hormone-sensitive lipase; ATGL, adipose triglyceride lipase; β3AR, β3 adrenergic receptors; mPTT-NCT, Prussian blue nanoparticle–based silk fibroin hydrogels; HSF1, heat shock factor 1; HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2/B1; SOD, superoxide dismutase; CAT, catalase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein cholesterol; ALOX15, Arachidonate 15-Lipoxygenase; 12(S)-HETE, 12(S)-hydroxyeicosatetraenoic acid; p38 MAPK, p38 mitogen-activated protein kinase; PAAu BPs, Gold nanoparticle bipyramids; PS, phosphatidylserine; GG-melanin, glycol-glycerol-melanin; AuNS, Gold nanospheres; AuNR, nanorods; Bax, Bcl-2-associated X protein; pTSLs, temperature-sensitive liposomes; HA, hyaluronic acid; HAuNS, hollow gold nanospheres; ATP, adipocyte-targeting peptides; BP, black phosphorus nanosheets; C/EBPα, CCAAT/enhancer-binding protein alpha; HIF-1, hypoxia-inducible factor 1; PI3K-Akt, phosphoinositide 3-kinase-Protein kinase B; EMN, effervescent microneedle; COA NPs, stearic acid-modified chitosan nanoparticles; Ahr, aryl hydrocarbon receptor; cNPs, cationic albumin nanoparticles; RSG, rosiglitazone; cAMP, cyclic adenosine monophosphate; PTEN, phosphatase and tensin homologue; AKT, protein kinase B; FoxO1, Forkhead box transcription factor O1; JNK, c-Jun NH2-terminal kinase; AS160, Akt substrate of 160 kDa; NO, nitric oxide; ICAM-1, intracellular adhesion molecule 1.

Data Sharing Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Disclosure

The authors declare no competing financial interests.

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