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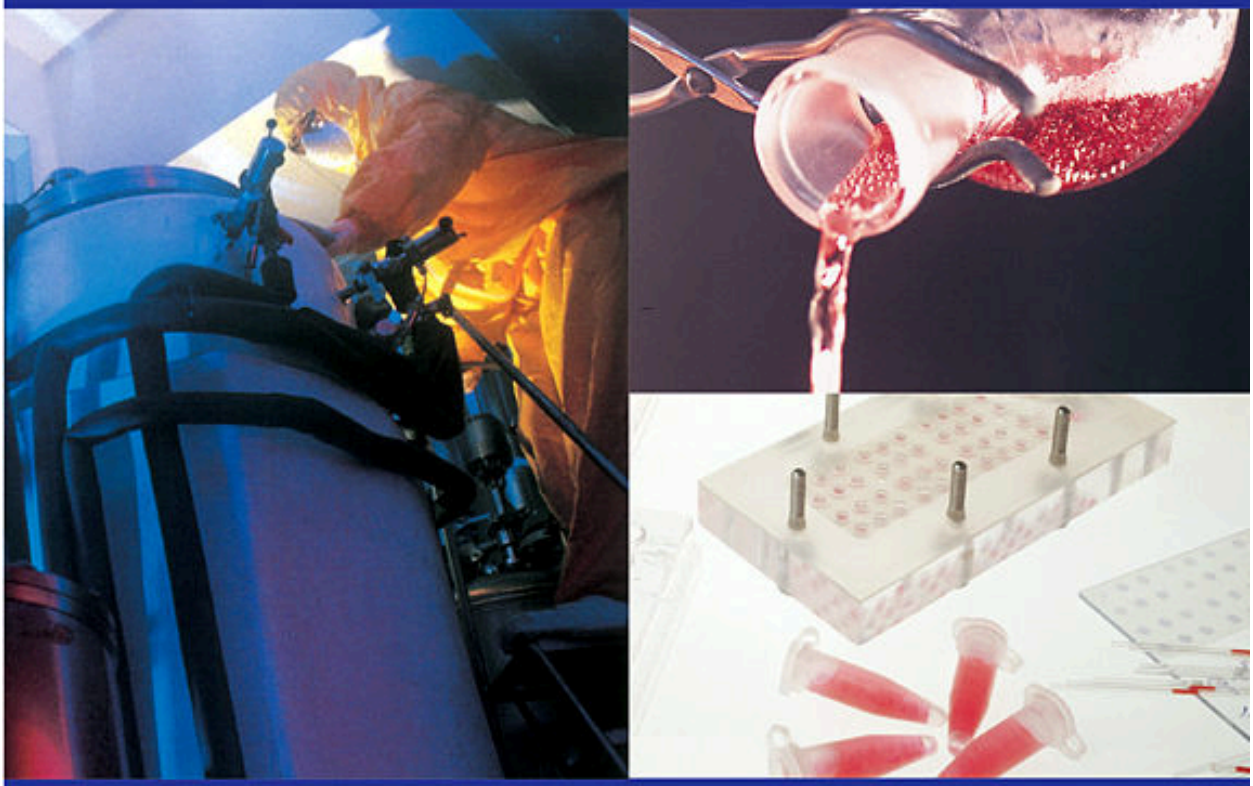

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Nutraceuticals enhanced by nanotechnology: A new frontier for obesity treatment

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ABSTRACT

Nutraceuticals encompass bioactive compounds like polyphenols, flavonoids, and essential fatty acids inherent in food that play defensive roles against human ailments. Presently, the pharmaceutical industry is focused on nutraceutical-based nanomaterials to mitigate drawbacks in obesity treatment. The use of nanomaterials enhances bioavailability, stability, and targeted drug delivery, diminishing side effects. This review delineates the significance, limitations, and molecular mechanisms of nutraceuticals' pharmacological properties, emphasizing how nutraceutical-based nanomaterials address challenges for effective obesity treatment. We outline potential nano-based anti-obesity drugs for heightened pharmacological impact and acknowledge associated clinical challenges and limitations. Critically, we evaluate the advantages and disadvantages of nutraceuticals, advocating various delivery systems to enhance their anti-obesity efficacy. Notably, nutraceutical-based nanoparticles offer increased bioavailability, precise distribution, reduced side effects, and prolonged sustainability, revolutionizing obesity management. Conscious implementation of nutraceutical-based nanoparticles holds promise in alleviating complications associated with conventional nutraceuticals in obesity management.

1. Introduction

Obesity is a global health concern, with an increasing number of people suffering from this condition. Over 1.9 billion persons worldwide were overweight in 2016, with over 650 million of those being obese, according to the World Health Organization (WHO) [1]. Since 1975, the prevalence of obesity has more than tripled, raising serious public health concerns. Additionally, more than 340 million kids and teenagers between the ages of 5 and 19 were either overweight or obese in 2016. Obesity is intricately linked to a multitude of serious health conditions including Type 2 diabetes, kidney failure, liver disease and so on, with the effects often stemming from the physiological changes induced by excess body fat [2]. Preventing and addressing obesity both reduces the risk of these associated health conditions and improves overall quality of life and well-being [3].

Natural substances called nutraceuticals are present in food and have positive impacts on health in addition to lifestyle measures like diet and exercise. Due to their perceived efficacy and safety compared to

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conventional weight-loss drugs, nutraceuticals, and nutraceutical-based techniques for the management of obesity have grown in favor over recent years [4]. Since ancient times, people have turned to herbal therapy as a safe and effective natural remedy for a range of illnesses, including obesity. However, there are several difficulties with treating obesity with natural medicines due to a lack of scientific evidence proving the efficacy of many of these treatments [5]. Furthermore, it can be difficult to identify the right dosage due to variances in quality and strength caused by the absence of standards in herbal goods. In addition, the safety profiles of these treatments are frequently less established than those of conventional pharmaceuticals, and they may have unanticipated adverse effects in combination with other medications[6]. Additionally, herbal medicines can have varying effects on different individuals and may not yield consistent or quick results [7]. They might not deal with the root cause for obesity for a long-term sustainable solution. Ultimately, it can be challenging to determine the true effectiveness of herbal medicines since people react to them differently and because the placebo effect may have an impact on their results. With respect to these, concerns regarding the safety and purity of these products are raised by the absence of quality control and regulation in the herbal supplement business. To ensure safety and efficacy within a comprehensive weight management plan, it is imperative to consult with a healthcare expert before adopting herbal therapies for treating obesity [8].

The main factors driving the nutraceutical market for obesity are the increased desire for natural and plant-based products, expanding knowledge of healthy lifestyles, and growing worries about the adverse effects of synthetic medications. Foods or dietary components with medicinal value known as nutraceuticals that offers additional health benefits beyond those offered by basic nutrition. Nanotechnology can be used to develop new features and functions at the nanoscale (1–100 nanometers) by manipulating materials. The rising prevalence of obesity and related medical conditions like diabetes, cardiovascular disease, and cancer is also fueling the demand for nutraceutical products [7].

Despite these advances, limited clinical translation of nanoformulations and insufficient mechanistic understanding of their anti-obesity effects remain unresolved. While prior reviews address nutraceuticals for obesity, critical gaps remain: (1) limited focus on food-derived nanomaterials, (2) underexplored molecular mechanisms of nano-enhanced nutraceuticals, and (3) minimal discussion of clinical translation barriers. This review bridges these gaps by analyzing nanoformulations of dietary phytochemicals, their mechanistic advantages, and challenges in regulatory approval.

Obesity's complexity demands innovative solutions. Recent advances in nanotechnology enable precise delivery of bioactive compounds, overcoming limitations of conventional nutraceuticals. Nanotechnology shows great promise in addressing the challenges of nutraceuticals, such as improving the distribution, absorption, and bioavailability of bioactive substances [9]. Nutraceuticals and nutraceutical-based nanoparticles have made major advances recently in the control of obesity, and these developments have many benefits. Significant advancements, including the use of nutraceutical-based nanoparticles, have been made in combating obesity through regulating metabolism, suppressing hunger, and promoting fat metabolism [10]. These substances can be made into nanoparticles with tailored distribution to tissues and increased bioavailability, which will increase their efficacy even further.

The creation of nanoemulsions is one method that nanotechnology can be used in nutraceuticals. Nanoemulsions, which can include hydrophobic bioactive substances like curcumin or resveratrol, are persistent suspensions of droplets with a size range of 20–200 nanometers [11]. These nanoemulsions can increase the compound's solubility and stability, increase their bioavailability and absorption, and deliver them specifically to tissues or cells [12]. The incorporation of nanoparticles as transporters/delivery system for nutrients and bioactive substances is another way that nanotechnology is used in nutraceuticals. These nanoemulsions offer controlled release, reduce gastrointestinal side effects (e.g., irritation) via targeted adipose tissue delivery and may lead to safer anti-obesity treatments [13]. Additional benefits include better palatability, suitability for combination therapies, and reduced doses for non-invasive administration [14]. Nanoparticles, such as those made from chitosan or biodegradable polymers, encapsulate and protect vitamins, minerals, and antioxidants, enhancing their stability and absorption in the digestive system. These technologies open up avenues for targeted and personalized nutrition, boosting the effectiveness and safety of nutraceutical products [15].

Even though prior reviews of nutraceuticals and nutraceutical-based nanoparticles in the management of obesity have been published on various aspects, there are very few on food derived nutraceutical-based nanomaterials for obesity [16–18]. A comprehensive understanding of phytochemicals, their molecular mechanism, and the problems associated with nutraceutical anti-obesity effects is highlighted in this review as critical in selecting nutraceuticals for nanoparticle synthesis Fig. 1a. We have also provided a critical update about the importance and drawbacks of nutraceuticals and how nutraceutical-based nanoparticles combat obesity by providing emphasis on greater bioavailability, tailored distribution, fewer side effects, and long-term sustainability. Further, we also highlighted the steps needed to be taken for the safety use of nutraceuticals and nutraceutical-based nanoparticles in clinical practice. Overall, we conclude that the application of nutraceutical-based nanoparticles can completely change how we address the complicated problem of obesity using nutraceuticals and help make the world's population healthier.

2. Importance of herbal nutrition in obesity management

The existing array of anti-obesity commodities available can be categorized into three primary classifications: (1) food-based constituents, (2) herbal extracts, and (3) alternative functional supplements. Among these, the development of functional supplements derived from commonplace dietary elements is significant within the industry. Specifically, items fashioned from fruits (such as citrus and berries), grains (like soybean), vegetables, or beverage extracts (such as tea leaves) tend to garner greater consumer trust due to their perceived safety and acceptability [19]. Citrus fruits stand out as a prominent category in the pursuit and utilization of novel anti-obesity formulations. Phytochemicals, namely triterpenoids, flavonoids, and alkaloids, emerge as promising ingredients present in both the peel and pulp of citrus fruits. Preclinical investigations involving cellular and animal models have revealed the anti-obesity properties of citrus fruit extracts, demonstrating their efficacy in reducing body weight gain and adipose tissue mass [20]. Notably, the consumption of citrus fruits has been associated with a reduction in leptin levels, a pivotal hormone produced by adipocytes crucial in regulating food intake and energy expenditure. Recent studies highlighted that methoxylated flavones and flavanone glycosides, key bioactive flavonoids in citrus fruits, modulate plasma leptin levels by inhibiting adipogenesis and enhancing lipolysis [21]. Herbal nutrition, the practice of utilizing plants and herbs as sources of nutrients and bioactive substances for promoting health and wellness, has been an integral part of traditional medical systems such as Ayurveda, Traditional Chinese Medicine (TCM) and Unani medicine for millennia [22]. Fig. 1**a** further summarizes the various sources of phytocompounds or nutrients with their potential activities for the management of obesity.

Over time, an expanding body of scientific research has underscored the efficacy of specific herbs and their bioactive compounds in addressing conditions like obesity. From ancient times, plants have served as conventional and natural remedies in the realm of pharmaceutical treatments. Today, pharmacological assistance includes viable alternatives known as phytomedicines, which are derived from plants. Phytomolecules, secondary metabolites obtained from plants, both exert pharmacological or toxicological effects on humans and animals and

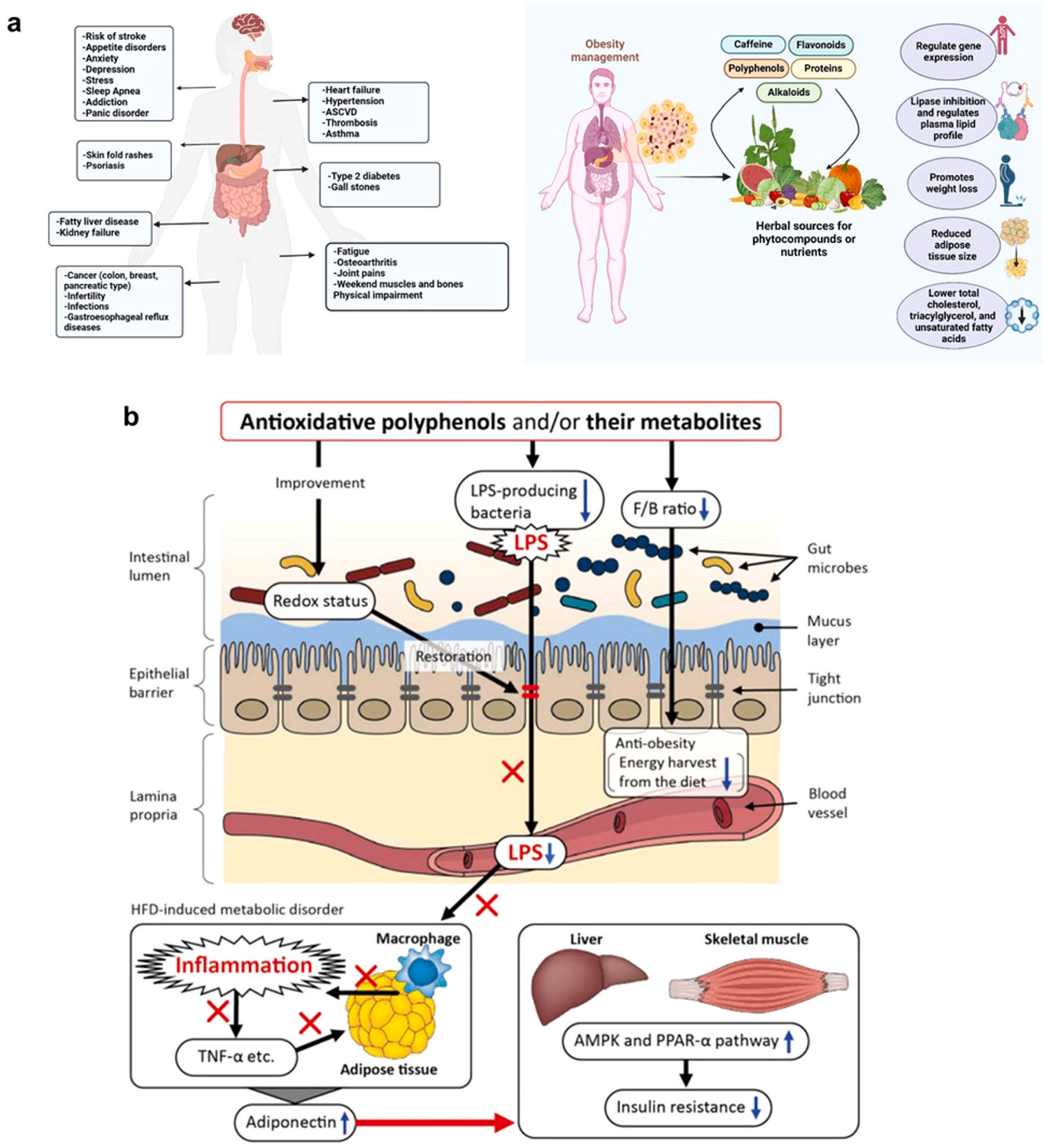

Fig. 1. a. Summary of various phytocompounds and nutrients from herbal sources, their role in the management of obesity and its complications in the human body (*created with biorender.com*). b. The proposed mechanism underlying the beneficial effects of polyphenols on metabolic disorders in high-fat diet (HFD)-fed murine models. Lps: lipopolysaccharide; ROS: reactive oxygen species; F/B ratio: Firmicutes/Bacteroidetes ratio; aMPK: aMP-activated protein kinase; PPAR-α: peroxisome proliferator-activated receptor-α. this figure has been reprinted with permission from ref [23], copyright 2022, MDPI.

interact with gut microbiota to modulate metabolic pathways critical for obesity management [24]. A myriad of plant-based products, consisting of isolated natural compounds and crude extracts, have demonstrated efficacy in combating diet-induced obesity and facilitating weight loss. Given the escalating global health threat posed by obesity, scientists and researchers are intensifying efforts to develop potent anti-obesity agents [25]. However, research on herbal plants faces constraints due to limited funding compared to pharmaceuticals. Plant-derived supplements typically contain a diverse array of phytochemicals, fostering additive or synergistic interactions. The attraction towards herbal therapy for obesity treatment stems from several factors. For example, patients often perceive herbal remedies as inherently safer than prescribed drugs. While herbal treatments may not require prescriptions, professional guidance is critical to avoid risks like drug interactions, improper

dosing, and long-term toxicity [26]. Additionally, advancements in nanotechnology have enabled the encapsulation of herbal bioactives into nanoparticles, enhancing their bioavailability and therapeutic efficacy while minimizing adverse effects.

3. Mode of action of important herbs in obesity management

Obesity is a global health issue that is regarded as a major cause of disorder and mortality. Because of its high caloric and intramuscular fat content, a high-fat diet (HFD) is associated with weight gain and obesity. Plant extracts contain multiple polyphenols, which have been recommended as a promising strategy for preventing obesity and related illnesses. Fig. 1**b** illustrates the proposed mechanism of polyphenols in high-fat diet-induced metabolic disorders**.**

3.1. Moringa oleifera

Moringa oleifera is a common herb that has been extensively applied in traditional medicine. It is known as "the miracle tree" because of its diverse pharmacotherapeutic potentials and it has rich nutritious value [27]. It belongs to the family Moringaceae, which contains large amounts of phytoconstituents and minerals.

3.1.1. Phytochemicals

Phenolic components like gallic acid, chlorogenic acid, caffeic acid, rutin, kaempferol, p-coumaric acid, vicenin-2, and quercetin were present in Moringa leaves, and the leaves were also reported to yield unique isothiocyanates, which are highly stable due to the presence of an excess sugar moiety in its structure [28]. Moringa flowers, roots, fruits, and seeds also contain phytochemicals such as vanillin, omega fatty acids, carotenoids, ascorbates, tocopherols and moringine. *M. oleifera* also contains two novel pyrrole alkaloid glycosides such as marumoside A and marumoside B, as well as pyrrolemarumine-4″-O-L- rhamnopyranoside, and the leaves and seeds contain β-sitosterol [28]. Table. 1

3.1.2. Pharmacological activities

These phytocompounds were reported to possess various pharmacological activities such as antioxidant, anticancer, immunomodulatory, anticarcinogenic, antidiabetic, antiatherogenic and hepatoprotective functions and participate in the regulation of thyroid biological functioning with anti-ulcer, antiepileptic, anti-allergic and anti-pyretic and anti-obesity effects. *M. oleifera* has significant therapeutic anti-obesity potential. *M. oleifera* contains anti-obesity compounds such as quercetin, isoquercetin, quercetin-3-O-malonylglucoside and astragalin [51, 52].

M. oleifera was shown to reduce body weight gain, relative epididymal, perirenal, mesenteric fat weight and fat tissue size, hepatic fat accumulation, and level of aspartate aminotransferase (AST) [53]. It decreased cholesterol, LDL, and TG level and improved HDL levels. This suggests that *M. oleifera* leaf extract possesses hypolipidemic and anti-obesity properties that could prevent the body from the negative consequences of a high-fat diet-induced obesity. Furthermore, intake of *M. oleifera* leaf extract on a regular basis could help to reverse hepatic steatosis and non-alcoholic fatty liver disease. *M. oleifera* was also reported to show promising effects in reducing hyperleptinemia, hyper-resistinemia and hypoadiponectinemia in obese rat serum. A recent study showed that *M. oleifera* leaves are effective in improving impaired insulin sensitivity and dyslipidemia in C57BL/6 L mice fed a high-fat diet [54]. *M. oleifera* had a hepatoprotective effect on the livers of obese female rats followed by a significant decrease in blood ALT (alanine aminotransferase) and AST (aspartate aminotransferase) enzyme activity.

M. oleifera was found to improve high fat diet induced consequences such as increased serum glucose, tissue insulin resistance and leptin levels and increased homeostasis model assessment-estimated insulin resistance (HOMA-IR) [55]. Polyphenolic components are reported to be very effective in scavenging and inhibiting ROS generation. As *M. oleifera* is rich in polyphenolic content, it could exhibit anti-obesity and antioxidant properties, which helps to overcome the negative effects of a high-calorie diet. *M. oleifera* was also reported to suppress endogenous oxidative stress and balance the antioxidant level in the liver, which improves hyperglycemia, insulin resistance and leptin levels. Insulin resistance develops because of a high-fat diet and increased generation of reactive oxygen species (ROS). *M. oleifera* can scavenge superoxide dismutase and catalase, thereby providing protection against oxidative stress and ROS and increasing total antioxidant capacity in the livers of obese rats. Thus, *M. oleifera* was reported to have a prophylactic effect against HFD-induced metabolic disturbance via restoring the level of antioxidants and ROS levels. The miracle tree provides an efficient protective mechanism in the liver of obese patients and high diet fat conditions by reducing nitric oxide generation, which enhances glucose metabolism through the GLUT transporter and stimulates mitochondrial biogenesis [55]. Interestingly, *M. oleifera* oil extract increased HDL levels. In diet-induced obesity of male rats, *M. oleifera* oil extract was also shown to improve oxidative stress and male reproductive markers.

In cases of obesity and its negative repercussions, improving redox balance pathways is a good therapeutic option. The nature of *M. oleifera* as an antioxidant is a direct plausible mechanism for explaining the therapeutic action of *M. oleifera* in alleviating the documented metabolic derangements. In addition, the new findings suggest the expression levels of visceral adipose tissue adipokines and their role in causing or/and improving the metabolic syndrome. *M. oleifera* is also capable of down regulating leptin and resistin mRNA expression, which could be related to the adiposity pathway and it is considered to have a thermogenic effect on adipose tissue [28]. Enhanced mRNA expression of the adipokines in the obese group supplemented with *M. oleifera* helps explain the mechanism of reduction in body weight and abdominal circumference [54], reduction in waist circumference, Lee index, BMI, and dietary habits, as well as reversing HFD-induced endothelium dysfunction [53]. In adult male long Evans rats fed with HFD, administration of powdered Moringa dry leaves had a substantial impact on anthropometric measures.

In an *in vitro* study of 3T3-L1 adipocytes, the compounds Niazinin B and 2-(4-[α-L-rhamnosyloxy) benzyl] isothiocynate from MO seeds [52] were able to inhibit intracellular fat accumulation. Another bioactive compound Astragalin from Moringa leaves were found to suppress TC (Total Cholesterol) and fat accumulation [52]. Astragalin's anti-obesity effect and stimulation of the β-adrenergic receptor pathway had previously been reported, although the evidence was limited [56]. An *in vivo* study reported that benzylamine, another compound suppressed the lipid peroxidation markers in C57BI6 male mice [57]. In 3T3-L1 cells, Moringa extracts were found to promote apoptosis by BAX upregulation and decreased BCL-2 expression, increasing caspase-3 activity and displaying nuclear condensation [51]. Apoptosis in adipocytes reduces fat mass by promoting programmed cell death, a mechanism exploited by compounds like resveratrol to counteract adipose tissue expansion. In 3T3-L1 cells, MO leaf extract lowered cellular lipid levels and decreased expression of PPAR, FAS, and ACC and CCAAT/enhancer-binding protein alpha (C/EBPα). Furthermore, petroleum ether MO leaf extract dramatically decreased the expression of PPAR, C/EBP, C/EBP, and FAS, while considerably increasing the expression of hormone-sensitive lipase (HSL) and the degree of phosphorylation of AMP-activated protein kinase (AMPK) and ACC [58]. Quercitrin, isoquercitin, and chrysin-7-glucoside have all been postulated as potential adipogenesis regulators found in MO.

One of the ways of regulating lipid levels is to inhibit pancreatic lipase. Because pancreatic lipase is crucial in fat metabolism, blocking the enzyme prevents lipids from being broken down, leading to a reduction in lipid monomer absorption and, as a result, a reduction in fat storage. Moringa leaves showed promising pancreatic lipase inhibition [59]. Moreover, [60] showed that Moringa and Moringa concentrate, which are rich in isocyanates, boosted lipolysis and thermogenesis,

Table 1
Anti-obesity effects of herbs and their components.

Herb	Family	Anti-obesity Component	Distribution	Models	Outcome	Reference
Nigella sativa	Ranunculaceae	Thymoquinone (TQ),	Albania, Bosnia, Bulgaria, Cyprus, Indonesia, Thailand, Singapore, India, Pakistan, Turkey, and Syria	Humans	Prevents obesity by regulating triglyceride levels and appetite suppression. It also has a big impact on the body's production of the hormone adiponectin, which is essential for preventing insulin resistance.	[29]
Hibiscus sabdariffa	Malvaceae	anthocyanins, flavonoids, and organic acids	India, Malaysia, China, Thailand, Sudan, Nigeria, Jamaica	Humans	Reduces fat buildup and oxidative damage while improving insulin sensitivity and resistance. In obese rats, the removal of visceral adipose tissue lowers inflammatory cytokines and the oxidative state, which improves insulin sensitivity.	[30]
Ilex paraguariensis	Aquifoliaceae	Quercetin, rutin, chlorogenic caffeic acid	South America (Brazil, Argentina)	Humans	Targets obesity and aids in the regulation of insulin by suppressing the expression of genes that control adipogenesis, enhancing the lipid profile, and functioning as an appetite suppressant.	[31]
Rosmarinus officinalis	Lamiaceae	carnosic acids	Mediterranean	Humans	The primary mechanism by which rosemary extract reduced weight gain and adiposity index appears to be limiting lipid absorption, as evidenced by the inhibitory effect of rosemary extract on gastric lipase activity and pancreatic lipase activity, two essential enzymes in the digestion and absorption of fat.	[32]
Coffea arabica	Rubiaceae	3-CQA (caffeoylquinic acid)	Ethiopia	Humans	Leptin and adiponectin, which regulate adipose tissue lipolysis, significantly lower body weight increase and white adipose tissue (WAT) weights.	[33]
Aframomum melegueta	Zingiberaceae	vanilloids such as 6-paradol and 6-gingerol	West African coast of Nigeria	Humans	6-Paradol and 6-Gingerol specifically regulated numerous gene expressions and AMPK phosphorylation in the liver and adipose tissue.	[34]
Panax ginseng	Araliaceae	ginseng saponins	East Asia (Korea, China, and Japan)	Humans	Ginseng reduces blood sugar and lowers blood lipase activity, which limits the digestion and absorption of both carbohydrates and fats and improves fecal weight.	[35]
Caralluma fimbriata	Asclepiadaceae	pregnane glycosides	India, Pakistan, and Afghanistan	Humans	It is hypothesized that pregnant glycosides prevent citrate lyase from accumulating fat. Malonyl coenzyme A is also inhibited, which further hinders the metabolic pathway's ability to synthesize fat. It stops the growth of new fat cells by interfering with malonyl coenzyme.	[36]
Capsicum annum	Solanaceae	capsaicin	Mexico	Humans	Capsaicin significantly decreased the glycerol−3-phosphate dehydrogenase (GDPH) activity and intracellular triglyceride in 3T3-L1 adipocytes by suppressing the expression of PPAR-, C/EBP-, and leptin.	[37]
Zingiber officinale	Zingiberaceae	6-gingerol and 6-shogaol	Southeast Asia, the Indian subcontinent, China, and New Guinea.	Humans	Reduced pancreatic lipase and amylase activity, which lowers plasma and tissue lipid levels.	[38]
Camellia sinensis (Green tea)	Theaceae	Epigallocatechin−3-gallate	China, East Asia	Mouse	Reduced adipose tissue size, fat mass, and body weight	[39]
Cinnamomum verum (Cinnamon)	*Lauraceae*	Cinnamaldehyde	Sri Lanka, Southern India	Rat	Reduced food consumption, body weight growth, and visceral fat mass	[40]
Curcuma longa (Turmeric)	Zingiberaceae	Curcumin	Subtropical regions	Mouse	Reduced adipose tissue size, fat mass, and body weight	[41]
Allium sativum Garlic	Amaryllidaceae	Allicin	South Asia, Central Asia and northeastern	Rat	Reduced body fat mass and weight gain	[42]
Piper nigrum (Black Pepper)	Piperaceae	Piperine	Western Ghats of Kerala, India, South-East Asia	Rat	Decreases in adipose tissue weight and body weight increase	[43]
Ocimum tenuiflorum (Holy Basil)	Lamiaceae	Ursolic acid	Philippines, Indonesia, African countries	Rat	Reduced adipocyte size, fat mass, and body weight gain	[44]
Trigonella foenum-graecum (Fenugreek)	Fabaceae	Trigonelline	Southeastern Europe and West Asia	Rabbits	Reduced food consumption, body weight growth, and fat mass	[45]
Taraxacum (Dandelion)	Asteraceae	Taraxasterol	Eurasia, America, Africa, New Zealand and Australia	Mice	Reduced body weight increase and smaller adipocytes	[46]
Nelumbo nucifera (Lotus Leaf)	Nelumbonaceae	Nuciferine	China, India, Russia, and Australia	Rats	Decreased adipocyte size, body weight, and fat mass	[47]
Ganoderma lingzhi (Reishi Mushroom)	Ganodermataceae	Polysaccharide peptide (PSP)	China, Japan, and Asian Countries	Mice	Body weight, fat mass, and adipocyte size were all reduced	[48]

(*continued on next page*)

Table 1 (*continued*)

Herb	Family	Anti-obesity Component	Distribution	Models	Outcome	Reference
(Aspalathus linearis) Rooibos	Fabaceae	Aspalathin	South Africa	Rat	Reduced adipocyte size, food intake, and body weight increase	[49]
Gynostemma Pentaphyllum	Cucurbitaceae	Gypenoside	China	Mice	Reduced plasma lipid levels, fat mass, and body weight	[50]

thereby reducing the fat accumulation as well as body mass. Because of its anti-inflammatory characteristics, adiponectin is an antiatherogenic drug that reduces cardiovascular risk. Because it lowers the expression of "LDL scavenger receptors" on macrophages, it decreases endothelial adhesion and dysfunction, decreasing LDL uptake and atherosclerosis formation [61]. Thus, *M. oleifera* can be exploited as a powerful phytotherapy agent in terms of improving hypercholesterolemia, atherosclerosis, and type 2 diabetes associated with obesity while avoiding adverse effects and hepato-toxicity. Numerous studies are in progress where Moringa-focused anti-obesity activity is being studied. This could help us better understand the components of MO that have anti-obesity properties.

3.2. Phyllanthus emblica

Emblica offcinalis Gaertn. syn. *Phyllanthus emblica L.*, known as 'Amla' or 'Aonla' or 'Indian gooseberry. It is a reservoir of nutraceuticals. Due to its high immune boosting efficiency, *P. emblica* has been broadly used in Indian traditional systems of medicine [62]. In Ayurveda, amla is considered to be a potent rejuvenator and immunomodulator effective in delaying degenerative processes and senescence. It promotes longevity, enhances digestion, treats constipation, reduces fever and cough, alleviates asthma, strengthens the heart, benefits the eyes, stimulates hair growth, improves the overall wellbeing of body, and enhances intellect.

3.2.1. Phytochemical composition

P. emblica is rich in iron, calcium, carotene, niacin, phosphorous, riboflavin and thiamine. Phytochemicals like Apigenin, gallic acid, ellagic acid, chebulinic acid, quercetin, chebulagic acid, corilagin, isostrictiniin, methyl gallate, luteolin, rutin, quercetin and other beneficial components are found in this herb. Emblicanin-A and Emblicanin-B (two low molecular weight hydrolyzable tannins) are present in *E. offcinalis* fruits, together with pedunculagin and punigluconin [63]. The principle active components of this fruit are tannins, gallic acid, and pyrogallol. Roots of *E. officinalis* contain three norsesquiterpenoids, such as phyllaemblicin-A, B and C and phyllaemblic acid along with bisabolene-type sesquiterpenoids like phyllaemblic acid B, phyllaemblic acid C and phyllaemblicin D with phenolic glycosides, 2-carboxylmethylphenol 1- O-β-d-glucopyranoside and 2,6-dimethoxy-4-(2-hydroxyethyl) phenol 1-O-β-d-glucopyranoside. Leucodelphinidin, tannin, and proanthocyanidin were found in the bark. Ellagic acid and lupeol are found in the roots. Phenolic concentration is greater in the pulp, whereas tannins are the most abundant element in *E. officinalis* seeds. Coumaric acid, myricetin, caffeic acid, and synergic acid are identified in both the pulp and seeds of *E. officinalis*; however, gallic acid and quercetin were reported to occur only in the pulp rather than the seed [64].

3.2.2. Pharmacological effects

The multifaceted ethnopharmaceutical importance of *P. emblica* is being exploited in various polyherbal preparations, and it helps to fight against various diseases. *E. offcinalis* fruits are one of the richest natural sources of vitamin C, which aids in the treatment of a wide range of illnesses [64]. They are beneficial in the treatment of dyslipidemia cancer, chronic periodontitis, dental caries, hyperacidity, hypertension, inflammation, iron deficiency anemia, neurological disorders, obesity, osteoporosis, pulmonary tuberculosis, skin diseases, Type 2 diabetes, Type II hyperlipidemia, vitiligo, and lifestyle diseases, as well as parasitic and other infectious disorders [65].

Amla fruit possesses significant pharmaceutical active agents like antihyperlipidemic, hypolipidemic and anti-atherogenic effect. For instance, *P. emblica* were reported to significantly suppress total cholesterol (TC), low-density lipoprotein (LDL), triglyceride (TG) and very low-density lipoprotein (VLDL) levels and cause an increase in high density lipoprotein (HDL) in type II hyperlipidemia patients. It also has the ability to cause a reduction in atherogenicity, and *in vivo* studies showed the hypolipidemic effects of *P.emblica* on the experimentally induced hypercholesteremic rats [66]. Inhibition of hepatic 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase and increased lecithin-cholesterol acyltransferase resulted in hypolipidemic action (LCAT). Flavonoids, which impede the synthesis and breakdown of lipids, are responsible for this effect. *E. officinalis* lowered total cholesterol, LDL cholesterol, and highly-sensitive C-reactive protein (hr-CRP) levels in class I obese adults. *E. officinalis* was also reported to have a repressing effect on HMG-CoA reductase activity, which is one of the major mechanisms involved in lowering cholesterol [67].

E. officinalis administration could reduce serum and hepatic cholesterol levels, serum triglyceride, phospholipids, and LDL-cholesterol level, which indicates its strong anti-atherosclerotic effect. Studies using *in vivo* models showed the hypolipidemic potential of *E. officinalis* was due to alterations in cholesterol absorption or enhanced enzymatic breakdown in hepatic tissues [67]. Saturated fats, in particular, promote a favorable energy balance and enhance lipid accumulation in the vasculature and around visceral organs. The cardiovascular system may be influenced by a high-fat diet via a direct, endothelial-dependent pathway and/or an indirect, cholesterol-dependent pathway. Research findings revealed that vascular anomalies were linked to a change in the endothelium L-arginine/NO pathway. Nitric oxide (NO) generation and/or release is a key endothelial factor in the regulation of vascular tone. *P. emblica* was reported to regulate endothelial dysfunction in high-fat diet induced rats [68].

P. emblica has been shown to have two properties: first, anti-adipogenic potential by downregulation of adipogenesis, and second, triggering apoptosis. Digallic acid was discovered to be the bioactive component in *P. emblica* fruit extract. The adipocyte-specific proteins ADIPOR1, FABP4, PPAR-γ, and the anti-apoptotic protein BCL2 were found to interact with digallic acid, which could be the cause of the ADIPOR1 cavity's robust stability through Pi-Pi and H-bonds interaction. A class of intracellular receptors known as fatty acid-binding proteins (FABPs) coordinates the trafficking of saturated and unsaturated fatty acids in cells [68]. FABP4 is a fatty acid-binding protein that is produced in mature adipocytes and plays a key role in the development of obesity and metabolic diseases. Digallic acid interacts with FABP4 in a way that is nearly analogous to co-crystal ligand interactions, thereby digallic acid exerts an inhibitory effect on FABP4 [68].

PPAR-γ is a key protein in adipocyte development and maturation. PPAR-γ is also a critical protein involved in lipid and cholesterol metabolism control. The use of *E. officinalis* could considerably increase hepatic PPAR-protein levels, which led to a decrease in cholesterol levels. Additionally, BAX was shown to be reduced but BCL-2 regulation was maintained in age-controlled rats *in vivo*. Additionally, *E. officinalis* caused a reduction in iNOS and COX-2 expression while up-regulating NF-κβ in rodent models [69]. Human clinical trials further support these findings. Administration of *E. officinalis* extract or whole fruit for 2–6 months reduced total cholesterol, LDL cholesterol, and VLDL

cholesterol in healthy and type-2 hyperlipidemic individuals. Long-term doses provide protection against atherosclerosis and related coronary artery diseases by lowering CRP, an inflammatory marker, while also increasing HDL levels and thereby maintaining normal physiology [70].

The anti-lipase action is one of the most well-studied ways of demonstrating natural products' decisive and long-term efficacy as anti-obesity treatments [71]. *P.emblica* fruit could inhibit pancreatic lipase more effectively. A new element in the treatment of obesity is the induction of apoptosis in mature adipocytes. Research involving *P.emblica* fruit extract was shown to cause enhanced cell death in differentiated cells as compared to control mature cells. This activation of the apoptotic pathway might be triggered by an imbalance between pro-apoptotic BAX and anti-apoptotic BCL-2 caused by increased caspase-3 activation. Thus, *P. emblica* offers anti-adipogenic potential through enhanced apoptosis and a suppressive differentiation pathway [72].

Increased fructose consumption in the diet has been identified as a potential cause of the development of obesity and related metabolic disorders in Western countries. Fructose consumption causes changes in several signaling pathways, including NF-κβ, TNF-α, JNK-1, PTP-1B, PTEN, LXR, FXR, and SREBP-1c [73]. The polyphenol-rich fraction of *E. officinalis* reduces metabolic changes caused by excessive fructose, such as SREBP-1 expression, total cholesterol, and TG levels. Increased mitochondrial MDA, COX-2, and BAX expression is inhibited by *E. officinalis*, which also regulates NF- κβ and BCL-2 expression in the liver [74]. Various research groups have recently demonstrated that treatment with *E. officinalis* increases lipid metabolism and reduces fructose-induced metabolic syndrome by up-regulating the expression of numerous proteins such as PPAR (which is involved in fatty-oxidation), FXR (which is involved in lipid metabolism), insulin-induced gene-2 (which prevents the maturation of SREBP-1) and steroyl CoA desaturase-1 (which is involved in the synthesis of TG). In addition, foam cell generation was considerably suppressed in RAW 264.7 cell lines, as was the expression of the CD36 scavenger receptor [64]. Thus, *P. emblica* could be regarded as a potent therapeutic medicine for obesity as it negatively regulates adipogenesis, induces lipid cell apoptosis and enhances HDL cholesterol.

3.3. Garcinia cambogia

Garcinia cambogia (Gaertn.) Desr syn. *G. gummi-gutta,* commonly known as Malabar tamarind, belongs to the Clusiaceae family, which has been extensively used in traditional medicine. *Garcinia* cambogia (GC) is used in Asia and Africa for its hypolipidemic, antidiabetic and anti-obesity effects.

3.3.1. Phytochemical constituents

Benzophenones, xanthones, and biflavonoids are the most abundant secondary metabolites in *G. gummi-gutta*. The major organic acid found in the fruit rinds of *G. gummi-gutta* is hydroxycitric acid (HCA). The fruit contains 10–30 % (-)HCA, which can be obtained as a free substance, a mineral salt, or a lactone. Benzophenones camboginol (garcinol) and cambogin (isogarcinol; xanthochymol) were present in latex of *G. gummi-gutta*. Barks contain garcinol, isogarcinol, garbogiol and rheediaxanthone A [75]. In contrast, leaves contains biflavonoids fukugicide, GB-1 and amentoflavone [76] and the oxy-guttiferones M, K2, I and K were found to be present in *G. gummi-gutta* fruits [75]. Xanthones from *G. gummi-gutta* were reported to possess diverse activities such as vasodilatory, antiviral activity, antimalarial, cytotoxic activity, human leukemia activity, α-glucosidase activity, CNS activity and platelet activating factor (PAF). Guttiferones and polyisoprenylated benzophenones from *G. gummi-gutta* were shown to exert leishmanicidal, cytotoxicity, anticancer, antifungal, antiproteolytic, and apoptotic activity as well as cytoprotection against HIV-1 *in vitro*. It also suppresses the binding activity of a-liver X receptor (LXRa). The bioactive compounds from *G. gummi-gutta* were found to possess anticholinesterase, antifungal, diuretic, anthelmintic, gastroprotective, hepatoprotective and antidiabetic properties [75].

3.3.2. Pharmacological activities

HCA is a vital substance for lifestyle and anti-obesity management. HCA is capable of significantly inhibiting the fatty acid and cholesterol biosynthesis. *In vivo* studies have confirmed the fat lowering potential of HCA without loss of protein content [77]. The mechanism of HCA for its anti-obesity activity includes serotonin regulation, reduced denovo regulation of lipogenesis, fatty acid oxidation, downregulation of a multitude of obesity-related genes and lowered insulin, leptin and glucose levels [75,77]. HCA exhibits anti-obesity properties and promotes weight loss by inhibiting the ATP-citrate lyase, which is one of the key enzymes for extramitochondrial cleavage of citrate to oxaloacetate leading to biosynthesis of fatty acid and cholesterol [77]. HCA depletes the acetyl-CoA and then malonyl-CoA pools, decreasing the availability of two carbon groups essential for fat and cholesterol production. Randomized human trials also showed the HCA ability to improve the blood lipid profile by suppressing the level of total cholesterol, LDL and triglycerides [77]. It also aids in the decrease of lipogenesis and regulates the serotonin levels. Scientific data based on Garcinia's structure, mechanism of action, and rich heritage of use has indicated a "no observed adverse effect level" (NOAEL) at doses up to 2800 mg/day, implying that HCA is safe to consume [77].

In cultured primary chicken hepatocytes, HCA lowers lipid droplet deposition through lowering acetyl-CoA supply and accelerating energy consumption [78]. HCA also mediates lipid metabolic processes through gene expression. That is, it stimulates peroxisome proliferator-activated receptor (PPAR) alpha and inhibits ATP citrate lyase (ACLY) and fatty acid synthase (FAS) mRNA expression, resulting in an elevation in fatty acid oxidation. An *in vivo* study reported that *G. cambogia* fruit rind could cause reduction in serum total cholesterol, triglycerol, glucose, insulin and leptin levels, triglycerides and LDL [79]. HCA supplements had a significant impact on body mass, body composition, and blood chemistry in healthy, overweight individuals, with a significant reduction in body fat but insignificant effects on BMI and several anthropometric parameters [80].

HCA caplet ingestion has a significant influence on weight, skin fold thickness (triceps, subscapular, midaxillary), cholesterol, triglycerides, HDL, and LDL levels in humans. HCA has been shown to boost protein synthesis in the liver and muscle by blocking fatty acid synthesis and shifting amino acid metabolic pathways. The HCA supplementation could diminish the triglyceride release into the blood stream and despite this drop, triglyceride levels in hepatic cells fall due to a reduction in synthesizing kinetics, which could imply the anti-lipogenic and pro-fatty acid oxidation and bile production properties of HCA [79].

Daily intake of HCA-SX (Salt of HCA) has proven to be helpful in lowering body weight and BMI in healthy and obese persons [79]. Gene expression studies, where genes that are required for mitochondrial/nuclear proteins and for adipose tissue, also provide evidence for the independent regulation of HCA-SX [77]. The salt also reduced the expression of genes encoding abdominal fat leptin in rats. Nonetheless, the appetite reducing activity of HCA-SX is thought to be mediated through a group of obesity regulating genes and reduction of [3 H]-5-HT release in the brain [77]. Dietary HCA-SX administration modulates a narrow group of genes (about 1 % of 9960 genes and ESTs) in adipocytes. HCA-SX had a specific effect on appetite reduction, with genes coding serotonin receptors being stimulated exclusively by the salt [77]. Neuropeptide Y (NPY) has recently been linked to HCA-induced anorexia. Supplementation with HCA-SX was alleged to cause a considerable reduction in the neurotransmitter's basal level in hypothalamic tissues. HCASX consumption elevated the genes for prostaglandin D synthase (PDS), aldolase B (AldB), and lipocalin (LCN2) in abdominal fat tissue. HCA was also able to induce a significant reduction in hunger, weight loss, and plasma leptin levels, as well as an elevation in serum serotonin and a favorable lipid profile [79]. Chronic treatment

of HCA improved enduring exercise performance in mice by reducing glycogen consumption induced by increased lipid oxidation during running exercise. The urinary concentrations of malondialdehyde (MDA), acetaldehyde (ACT), formaldehyde (FA), and acetone (ACON) were measured in a more current approach for detecting fat metabolism by HCA.

In vivo studies have shown that the fruit rinds of *G. combogia* were able to lower total cholesterol, triacylglycerol, and unsaturated fatty acids in the blood and regulating blood leptin and insulin. It also reduced dyslipidemia in HFD-induced obesity. In the epididymal fat tissue of treated rats, the expressions of leptin, tumor necrosis factor-alpha, and sterol regulatory element binding protein 1c genes were reduced. In addition to a reduction in food intake by *G. combogia* diet, the food efficiency ratio (FER) was considerably lower, reflecting a less effective conversion of feed mass into body mass. HCA and *Garcinia cambogia* may help with weight loss. However, clinical trials are needed to determine the best circumstances for HCA to work.

3.4. *Alpinia officinarum*

Alpinia officinarum, which belongs to the *zingiberaceae* family has rich therapeutic properties. The rhizome of this plant is referred to as Galangal (commonly known as lesser galangal). *Alpinia galanga* wild (Zingiberaceae) (AG) is a rhizomatous herb grown in Malaysia, India, Indochina, and Indonesia. It is widely used in India as a domestic remedy for the treatment of rheumatoid arthritis, cough, asthma, obesity, and diabetes. It was also reported to have anti-obesity, hypoglycemic, hypolipidemic and antioxidant properties.

3.4.1. *Phytochemical composition*

Numerous phytochemicals have been found to be associated with the herb, which includes Quercetin, kaemferol, isorhamnetin, galangin, kaemferide, alpinol, and galangol, galangin-3-methylether, rhamnocitrin and 7- hydroxy-3,5-dimethoxyflavone. Rhizome contains alpinol, galangol and tanningmaterial. Sorghumaol and bochmord have also been isolated from the herbaceous rhizomes. Anti-inflammatory, antibacterial, antifungal, antiviral, diuretic, and anticancer activities have been documented for the plant [81]. This plant's rhizomes are used as a culinary flavoring as well as an indigenous medicinal remedy for various ailments. Pancreatic lipase is a crucial enzyme for lipid breakdown and fatty acid absorption. 3-Methylethergalangin and 5-hydroxy-7-(49-hydroxy-39-methoxyphenyl)-1-phenyl-3-heptanone from *A. officinarum* have the ability to suppress pancreatic lipase and reduced serum lipid profile levels [81]. Weight lowering capacity of the *A. officinarum* could be due to the cumulative impact of various phytochemicals such as flavonoids and phenolics.

3.4.2. *Pharmacological activities*

The impact of polyphenols or flavonoids on lipid profiles are important in the treatment of cardiovascular disorders. *A. officinarum* were able to improve the lipid profile by decreasing blood total cholesterol, TG, and LDL-C concentrations, plasma leptin level, and the atherogenic factor. Furthermore, animal studies demonstrated ALT reduction, but human trials are needed for validation. *A. officinarum* tends to reduce the size of epididymal adipocytes, which are typically higher in obese people [81]. Several phytoconstituents in *A.officinarum* may play key roles in influencing lipogenesis and modifying body fat.

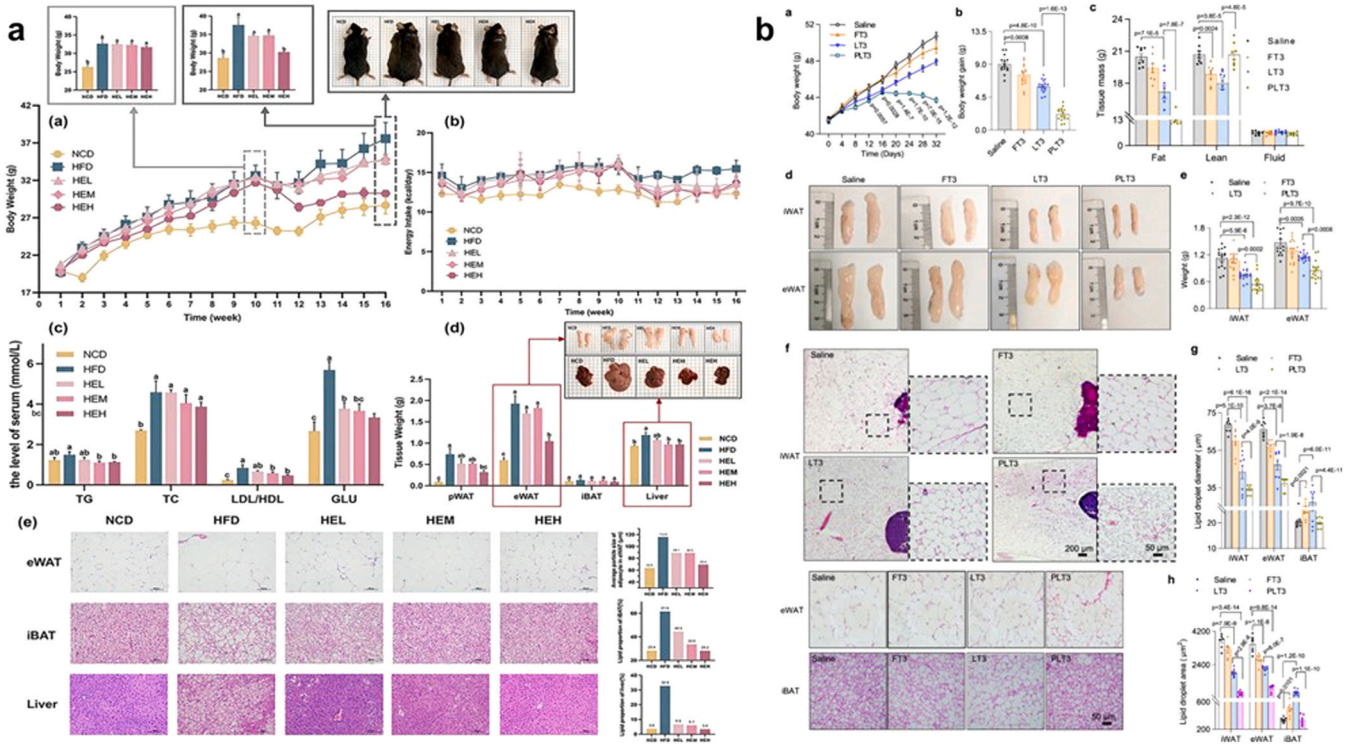

Fig. 2. A. Effects of (−) -epigallocatechin-3-gallate (EGCG) on high-fat diet (HFD)-induced obesity. (A) Weight gain in 16 weeks. (B) Energy intake. (C) Serum biochemical *p*arameters. (D) Tissue weight. (E) Hematoxylin-eosin staining of the adipose tissue and liver. Data are expressed as means ± SEM ($n = 5$). means with different letters (a–d) were considered significantly different at $p < 0.05$ according to tukey's test. *n*cd, mice on a *n*ormal chow diet with a daily water gavage; HFD, mice on a high-fat diet with a daily water gavage; HEL, mice on a high-fat diet with a daily EGCG gavage at the dose of 25 mg/kg; HEM, mice on a high-fat diet with a daily EGCG gavage at the dose of 50 mg/kg; HEH, mice on a high-fat diet with a daily EGCG gavage at the dose of 100 mg/kg; eWAT, epididymal adipose tissue; *p*WAT, *p*erirenal adipose tissue; iBAT, interscapular brown adipose tissue. In the body diagram in (A) and the tissue diagram in (D), the length of each small cell is 0.5 cm. *p*LT3 is more efficient than FT3 and LT3 in counteracting obesity and reducing adiposity.
(a) This figure and related contents were reprinted with permission from [82], copyright 2023, Frontiers.b. (b) Adapted from [117] with permission, copyright 2024, Nature.

3-Methylethergalangin isolated from the rhizome extract of *A. officinarum* acts as a pancreatic lipase inhibitor. *In vivo* studies on maize oil feeding-stimulated triglyceridemic mice and Triton WR-1339-induced hyperlipidemic mice could give us insight into the serum TG and cholesterol lowering effect of *A. officinarum* [81]. Similarly, green tea catechin epigallocatechin gallate (ECGG) suppresses body weight, fat accumulation, and liver steatosis [82] (Fig. 2a). Another phytocompound, galangin, suppressed pancreatic lipase activity *in vitro*, indicating that it has a lipid digestion and absorption limiting impact. Thus, its hypolipidemic efficacy is highly related to the pancreatic lipase inhibition. Animal models like cafeteria diet induced obesity showed the positive regulation of galangin on body weight, food intake, serum lipids, liver and PAT weight, hepatic lipid peroxidation, and liver TG concentration, which indicates the anti-obesity effect of *A. officinarum* [83].

3.4.3. Combination nanoformulations

To increase the anti-obesity effects of nutraceuticals, combination nanoformulations can be developed. For instance, a nanoemulsion made of curcumin and piperine has been demonstrated to have a synergistic effect in lowering body weight and fat mass in obese mice [84]. This synergy is not merely additive but involves complex molecular mechanisms that amplify the therapeutic impact.

Combination nanoformulations in biomedicine represent a cutting-edge approach in the development of advanced drug delivery systems. These formulations involve the encapsulation of multiple therapeutic agents, such as drugs or biologically active compounds, within nanoparticles to achieve synergistic effects or enhanced treatment outcomes [85]. Fig. 2a illustrates the effects of (−)-epigallocatechin-3-gallate (EGCG) on high-fat diet (HFD)-induced obesity. The data show that EGCG treatment at various doses significantly reduces weight gain, energy intake, and serum biochemical parameters compared to HFD controls. EGCG administration at higher doses (HEM and HEH) resulted in significantly lower weight gain over 16 weeks compared to the HFD group (Fig. 2a-A). This reduction was accompanied by decreased energy intake (Fig. 2a-B), indicating that EGCG may modulate appetite and metabolic rate. GCG treatment improved serum lipid profiles, as evidenced by reduced triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and increased high-density lipoprotein (HDL) levels (Fig. 2a-C). These changes suggest that EGCG influences lipid metabolism and reduces the risk of dyslipidemia associated with obesity. EGCG treatment led to reduced tissue weights of epididymal adipose tissue (eWAT), perirenal adipose tissue (pWAT), and interscapular brown adipose tissue (iBAT) (Fig. 2a-D). Histological analysis revealed smaller adipocyte sizes and reduced lipid droplet accumulation in eWAT and liver tissues (Fig. 2a-E), indicating that EGCG promotes lipolysis and inhibits adipogenesis. The molecular mechanisms underlying these effects involve the activation of peroxisome proliferator-activated receptors (PPARs), particularly PPARγ. PPARγ plays a critical role in adipocyte differentiation and lipid storage. EGCG may inhibit PPARγ signaling, thereby reducing adipogenesis and promoting lipolysis. Additionally, EGCG activates AMP-activated protein kinase (AMPK), which enhances fatty acid oxidation and glucose uptake in adipocytes and skeletal muscle cells.

By combining different therapeutic agents within nanoparticles, it is possible to achieve improved drug solubility, controlled release, and enhanced drug stability, leading to better therapeutic efficacy. For instance, Chen et al. [86] recently reported the encapsulation of T3 in liposomes modified with an adipose homing peptide (PLT3) significantly counteracted obesity compared to FT3 and LT3. Moreover, these formulations can minimize systemic toxicity and side effects, as they allow for the targeted delivery of multiple agents to specific tissues or cells (Fig. 2b). The targeted delivery of T3 via PLT3-liposomes results in enhanced thermogenesis and lipolysis in adipose tissues. T3 activates thyroid hormone receptors, which upregulate genes involved in energy expenditure and lipid metabolism. By concentrating T3 in adipose tissues, PLT3-liposomes maximize its therapeutic impact while minimizing systemic toxicity and side effects observed with FT3 and LT3 treatments. This innovative approach holds great promise in revolutionizing the treatment of various diseases and disorders by offering more effective, efficient, and precise therapeutic interventions.

Combination nanoformulations represent a cutting-edge approach in biomedicine, offering advanced drug delivery systems for treating complex diseases like obesity. These formulations enable the simultaneous targeting of multiple pathways or cellular processes, achieving synergistic effects and improved therapeutic outcomes. Further research should focus on optimizing the design and formulation of combination nanoformulations, elucidating their molecular mechanisms, and conducting long-term clinical trials to validate their safety and efficacy in real-world applications.

4. Challenges associated with herbal Medicine

Over the past few decades, there has been a notable shift towards eco-friendly and relatively safe herbal medicines, transitioning from the periphery to the mainstream. This evolution is largely attributed to the surge in research within the realm of traditional medicine. As more people explore all-natural, non-invasive alternatives to conventional drugs, the use of herbal medicine to treat obesity is growing in popularity. However, using herbal remedies to treat obesity has a number of drawbacks, including variable dosing, a lack of standardization, and potential side effects [87]. India boasts a vast repository of medicinal plants and holds the potential to rise to the challenge of meeting global demand for them. Ayurveda, Naturopathy, Unani, Siddha, and folk medicine form the cornerstone of healthcare systems in Indian society, all heavily reliant on natural resources [88]. The market for herbal drugs has witnessed significant growth, spurred by a resurgence of interest in traditional and alternative healthcare systems worldwide, thereby elevating the economic significance of medicinal plants. However, several challenges hinder the growth of herbal medicine. These include the loss of biodiversity, over-exploitation, and unscientific utilization of medicinal plants, as well as the pressures of industrialization and issues like biopiracy. Moreover, the absence of adequate regulation and infrastructure further compound these challenges, necessitating concerted efforts to address them effectively [88].

The complexity and variability inherent in the constituents of herbal medicines pose internal challenges that can impact their quality. However, strategies to address these issues have been explored. While adulteration and substitutions represent deliberate actions, misidentification occurs inadvertently. False authentication may arise when importers or retailers mistakenly confuse one herb for another due to incorrect labeling or the similar appearance of herbal materials. Confusing nomenclature can indeed contribute to misidentification. A single herb may be referred to by various names, including one or more common names, its Latin name, local names, and even brand names. Moreover, different medicinal herbs, stemming from distinct plant species and possessing disparate constituents, may share similar names, further complicating accurate identification. Implementing stringent protocols such as Good Agricultural and Collection Practices (GACP) and Good Manufacturing Practices (GMP) can significantly mitigate external factors that may compromise quality. The primary challenge lies in ensuring the knowledge, qualifications, and training of traditional medicine providers. It is imperative to provide comprehensive training to ensure that both traditional medicine practitioners and allopathic practitioners comprehend and value the complementary nature of healthcare systems [89]. Despite varying degrees of recognition by governments, urgent attention is required to address several key issues. First, the lack of robust scientific evidence regarding the efficacy of many traditional herbal medicine systems poses a significant hurdle. Additionally, safeguarding indigenous traditional knowledge and addressing concerns related to its proper utilization are pressing matters that demand immediate attention. By addressing these challenges,

strides can be made towards integrating traditional medicine into mainstream healthcare systems effectively and responsibly [90].

Furthermore, advancements in modern analytical methods and pharmaceutical techniques offer avenues to address previously unresolved internal challenges. By leveraging these tools, herbal medicine manufacturers can enhance consistency and standardization, thus improving the overall quality of their products.

4.1. Dosage variations

The challenge of obtaining regular dosages is one of the main drawbacks of using herbal remedies for obesity [26]. Herbal medications' efficacy and composition might vary based on a variety of circumstances, including soil quality, climate, and processing techniques, in contrast to pharmaceutical drugs, which are meticulously formulated and standardized. Consequently, it could be challenging to get dependable and consistent results. A multitude of environmental variables, ranging from soil composition and altitude to seasonal fluctuations in temperature, atmospheric humidity, length of daylight, and rainfall patterns, can significantly influence the concentration of components within any given batch of herbal products. Additionally, factors such as genetic variation, timing of seeding, utilization of pesticides and fertilizers, planting density, and other agronomic practices also have notable impacts on the final composition and quality of herbal materials [91].

4.2. Absence of standards

The absence of standards among various manufacturers and products is another issue with herbal medicine. The same governmental control that applies to pharmaceutical treatments also does not apply to herbal remedies. Therefore, there is no established testing or certification procedure to guarantee uniformity and quality.

4.3. Possibly adverse effects

The possibility for negative consequences, particularly when used in conjunction with other pharmaceuticals, is another drawback of herbal treatment. Certain herbal extracts may interact with other medications, leading to unanticipated and possibly harmful adverse effects. Additionally, some herbal extracts have the potential to produce allergic reactions or other negative side effects, especially if the dosage is not well monitored or the extracts are not standardized [92].

4.4. Optimizing Herbal-Nanotechnology integration

Obesity is a global health issue that is regarded as a major cause of disorder and mortality. Because of its high caloric and intramuscular fat content, a high-fat diet (HFD) is associated with weight gain and obesity. Plant extracts contain many polyphenols, which have been recommended as a promising strategy for preventing obesity and related illnesses. However, the variability in herbal extracts due to differences in cultivation, environmental conditions, and postharvest practices poses significant challenges to their standardization and efficacy.

To address these challenges, we emphasize the importance of standardization through rigorous phytochemical profiling, adherence to Good Manufacturing Practices (GMP), and robust quality control protocols. Nanotechnology plays a pivotal role in overcoming this variability by encapsulating bioactive compounds, thereby enhancing their stability, bioavailability, and therapeutic efficacy while preserving the intrinsic benefits of herbal extracts. This integration ensures consistent delivery of active ingredients, mitigating concerns about dosage accuracy and potency.

Furthermore, the synergy between nutritional components and traditional herbal medicine can prevent nutrient depletion and reduce potential adverse effects, making it an effective approach for holistic health management. By leveraging nanotechnology, we can optimize the delivery of herbal-based therapies, ensuring they meet modern safety and regulatory standards while maintaining their traditional healing properties.

5. Expand industrial applications of nutraceuticals

Nutraceuticals are natural substances with potential health advantages, and nanotechnology has emerged as a significant tool in their production. It is feasible to develop more potent and specialized treatments for a variety of medical problems by enhancing the pharmacological action of nutraceuticals using nanotechnology for industrial applications. In this section, we look at the application of nanotechnology to nutraceuticals and how it might lead to better pharmacological action.

5.1. Increased bioavailability of nutraceuticals

Enhancing bioavailability is one of the main benefits of employing nanotechnology in nutraceuticals. Numerous nutraceuticals have low bioavailability, which means that their therapeutic effects are constrained due to poor absorption by the body. Nutraceuticals can be shielded from oxidation and made more soluble by being enclosed in nanoparticles, which enhance absorption and bioavailability [93].

For instance, curcumin, a nutraceutical with strong anti-inflammatory and antioxidant activities, has low solubility and quick metabolism, which results in poor bioavailability. Curcumin can be made more soluble and protected from degradation by being enclosed in nanoparticles, which increases bioavailability and boosts pharmacological action [94]. Similarly, encapsulation of rosigliatazone using PLGA-PEG nanoparticles binds to angiogenic vessels through controlled release Fig. 3a, and by retaining rosigliatazone inside the nanoparticle core for transforming WAT into brown-like adipose tissue to stimulate angiogenesis.

Resveratrol nanoparticles have shown promise in a range of biomedical applications, including their use as antioxidants, anti-inflammatory agents, and for potential cancer prevention and cardiovascular health. The nano-sized particles provide a larger surface area for interaction with biological systems, allowing for more efficient absorption and targeted delivery (Fig. 3b). Moreover, resveratrol nanoparticles can address the challenges associated with the poor water solubility of resveratrol, ultimately improving its therapeutic potential. This approach may open new avenues for the development of advanced drug delivery systems and therapeutic strategies for various health conditions [97].

5.2. Delivery with specificity

Targeted delivery is another benefit of applying nanotechnology to nutraceuticals. Nutraceuticals based nanomaterials can be delivered directly to the site of action to target tissues or cells, which can increase anti-obesity efficacy and minimize negative effects of untargeted drug delivery. Untargeted drug delivery, where medications are not specifically directed to their intended sites of action, can have several negative effects on both the efficacy of treatment and patient well-being. This approach lacks the precision and selectivity that targeted drug delivery methods offer, resulting in a range of potential drawbacks. One of the most significant disadvantages of untargeted drug delivery is the increased risk of systemic side effects. When medications are distributed throughout the entire body, healthy tissues and organs may be exposed to the drug, leading to adverse reactions and complications [98].

One of the most significant disadvantages of untargeted drug delivery is the increased risk of systemic side effects. When medications are distributed throughout the entire body, healthy tissues and organs may be exposed to the drug, leading to adverse reactions and complications. To mitigate these risks, strategies such as surface modifications (e.g.,

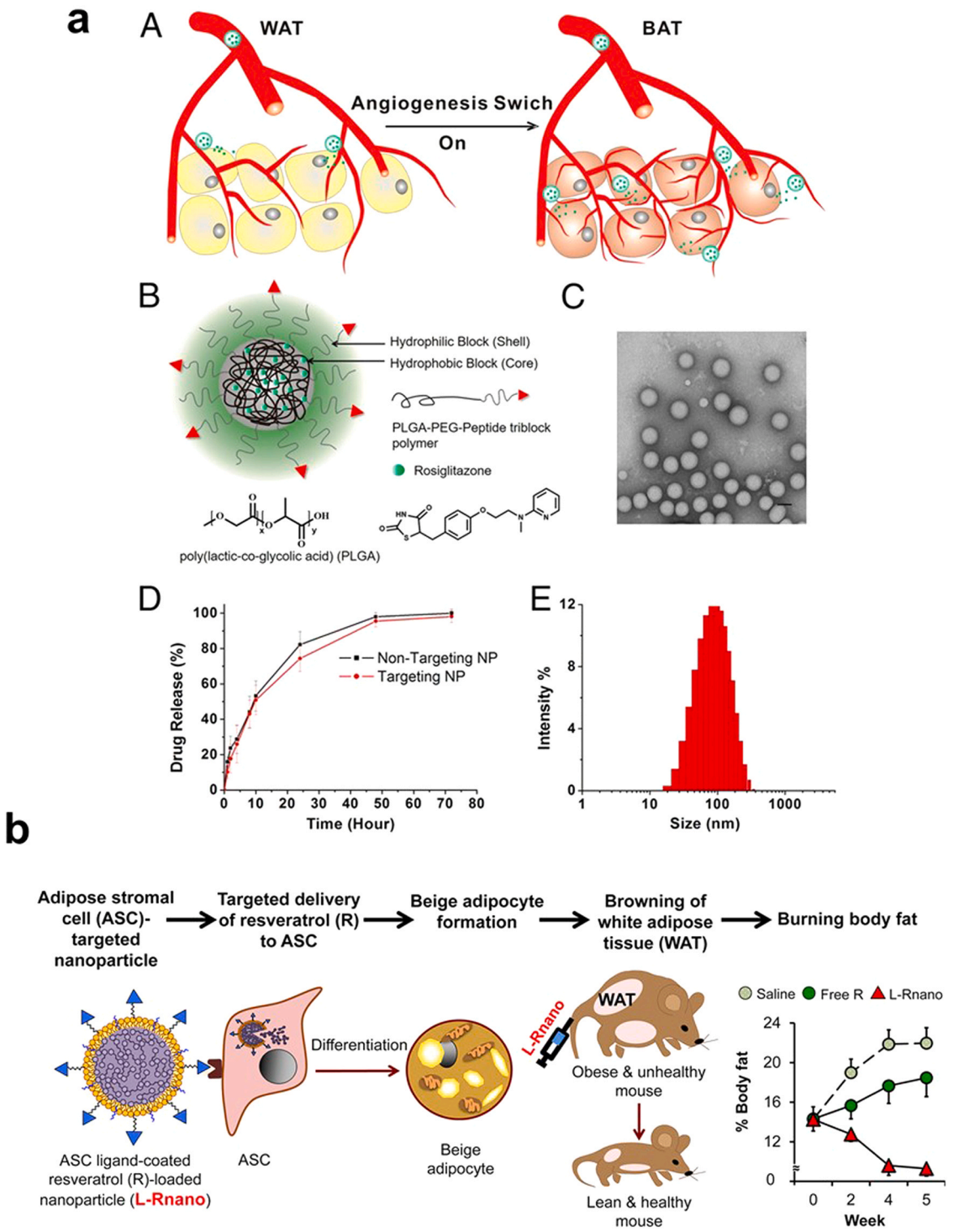

Fig. 3. A. Np design and characterization. (A) A schematic representation of the WAT browning process through a positive feedback drug delivery system. Released Rosi and PGE2 promote transformation of WAT into brown-like adipose tissue and stimulate angiogenesis. This facilitates the homing of targeted NPs to adipose angiogenic vessels, thereby amplifying their delivery and hence expediting the WAT browning process. (B) Chemical structure of PLGA-b-PEG-Peptide/Rosiglitazone NPs (NPs). the particle consists of two components: (I) an outer PEG surface with a targeting peptide iRGD or P3. b. Illustration of adipose stromal cell-targeted resveratrol-loaded nanoparticle structure, targeting and working mechanisms, and the anti-obesity effect in obese C57BL6/J mice.
(a) This figure was reprinted with permission from [95] copyright, 2016 by the National Academy of Sciences. (b) This figure was reprinted with permission from Ref [96], copyright, 2021, Elsevier.

polymeric coatings) and the use of biodegradable polymers like PLGA and chitosan have been introduced to enhance specificity and reduce off-target cytotoxicity. Untargeted drug delivery may necessitate higher drug doses to ensure that enough reaches the target site, resulting in decreased treatment effectiveness and a waste of pharmaceutical resources. By optimizing encapsulation efficiency and dose delivery, nanotechnology can significantly reduce the required dosage, thereby minimizing exposure to non-target tissues. It can also lead to a delay in the onset of action and potentially contribute to drug resistance. Furthermore, untargeted drug delivery can result in organ toxicity and

patient discomfort, potentially leading to non-adherence to treatment regimens. Surface charge alterations, such as using negatively charged ligands, have been shown to reduce nanotoxicity and improve biocompatibility. Overall, untargeted drug delivery lacks the precision and efficiency necessary for optimal therapeutic outcomes and can be associated with a range of negative effects on patients and treatment outcomes.

5.3. Enhanced stability

Additionally, nutraceutical stability can be enhanced by nanotechnology, which can support the preservation of their pharmacological efficacy over time. Numerous nutraceuticals can decay and lose their therapeutic properties because they are susceptible to environmental elements like light, heat, and oxygen. It is feasible to shield nutraceuticals from the environment and improve their stability by encapsulating them in nanoparticles [99].

When exposed to air or light, vitamin C, a nutraceutical with strong antioxidant qualities, can deteriorate very quickly. However, vitamin C can be shielded from deterioration and have its pharmacological effectiveness sustained over time by being enclosed in nanoparticles [100]. Similarly, various delivery systems has been used to improve low water solubility and stability lead to low bioavailability of lycopene [101]. There are various drug delivery systems used for the treatment of obesity to carry bioactive compounds for the effective delivery, decreased toxicity, increased water stability, improved biocompatibility, increased bioavailability, and biodegradability[102].

5.4. Blended therapies

The creation of combination medicines is another potential use for nanotechnology in nutraceuticals. The synergistic effects that can be produced by mixing nutraceuticals with various pharmacological activity in a single nanoparticle can improve therapeutic efficacy [103]. However, the pharmacokinetic changes induced by nanoparticles, such as altered absorption, distribution, and metabolism of bioactive compounds, must be carefully considered.

One such nutraceutical is epigallocatechin gallate (EGCG), which has strong anti-inflammatory and antioxidant activities but has a low bioavailability and a quick metabolism. By encapsulating EGCG in nanoparticles, its pharmacokinetic profile can be significantly improved, enhancing its therapeutic potential. However, by combining EGCG with other nutraceuticals like resveratrol and curcumin and encapsulating them in nanoparticles, it is possible to produce a combination therapy with higher pharmacological activity and improved therapeutic efficacy [104]. Despite these advancements, gaps remain in understanding tissue-specific biodistribution of nanoparticles. Future studies using advanced imaging techniques, such as PET scans, in preclinical models are needed to address these knowledge gaps.

6. Potential nano-nutraceutical based anti-obesity drugs

A wide range of new tools and opportunities, from early diagnoses and enhanced imaging to better, more effective, and tailored medicines, could be realized by the application of nanotechnology to medicine. This developing field may help in the fight against obesity thanks to developments in drug delivery, nutraceuticals, genetic and epigenetic therapies. Its use in treating obesity is still primarily in the development stage. Regarding the advantages and constraints of current nanotechnology techniques, we will now explore the innovative perspective of nanotech applied to human consumable items and their specific applications to combating obesity through nutraceuticals. We wrap up by talking about some previously developed nutraceutical-based nanomaterials for the treatment of obesity.

6.1. Curcumin nanoemulsion

Turmeric contains the polyphenolic compound curcumin, which has anti-inflammatory and anti-obesity properties. However, its ineffectiveness is constrained by its poor solubility and low bioavailability. The formulation of curcumin as a nanoemulsion increases its bioavailability and solubility. According to studies, curcumin nanoemulsion can help obese mice lose weight, adipose tissue mass, and inflammation [105].

Curcumin, a natural polyphenol found in the spice turmeric, has gained considerable attention in the field of biomedical applications due to its potential health benefits. One innovative approach to harnessing the therapeutic properties of curcumin is through the development of curcumin nanoemulsions. Nanoemulsions are colloidal systems in which curcumin is encapsulated in tiny droplets of oil and stabilized with surfactants, resulting in a formulation that enhances the solubility, stability, and bioavailability of curcumin [106]. These curcumin nanoemulsions have shown promise in a variety of biomedical applications, including anti-inflammatory, antioxidant, anti-cancer, and neuroprotective effects. The small droplet size and increased surface area provided by nanoemulsions enable curcumin to be absorbed more efficiently in the body, potentially leading to improved therapeutic outcomes. Research conducted by Abdulmalek et al. aimed at exploring the therapeutic potential of synthesized natural compounds, specifically curcumin nanoparticles (CurNPs) and zinc oxide nanoparticles (ZnONPs), to address hepatic and pancreatic pathophysiological changes induced by a high-fat diet (HFD) and streptozotocin (STZ) in type 2 diabetes mellitus (T2DM). This investigation involved assessing the impact of these compounds on the AKT pathway and MAPK pathway. The study suggests that administering 10 mg/kg of CurNPs and 50 mg/kg of ZnONPs demonstrates a superior anti-diabetic effect across all measured parameters compared to conventional curcumin and $ZnSO_4$, as well as the anti-diabetic drug metformin. The observed decrease in serum glucose and insulin levels is indicative of the potential mechanism involving the upregulation of the PI3K/AKT signaling pathway in hepatic tissue. Furthermore, these compounds demonstrate the ability to mitigate clinical manifestations of obesity onset, including inflammation, oxidative stress, and insulin resistance, likely through the inhibition of MAPK pathways. Notably, they also contribute to the alleviation of structural damage to the liver [107]. Furthermore, the use of curcumin nanoemulsions can overcome the inherent limitations of curcumin, such as its poor aqueous solubility and rapid metabolism. As a result, curcumin nanoemulsions have the potential to be a valuable tool in the development of novel drug delivery systems and therapeutic strategies for various health conditions [108].

6.2. Resveratrol nanoparticles

Red wine and grapes contain the polyphenol resveratrol, which has anti-inflammatory and anti-obesity properties. However, its effectiveness is constrained by its poor solubility and low bioavailability. Resveratrol can be made into nanoparticles utilizing polymeric substances that increase its solubility and bioavailability, such as chitosan or poly(lactic-co-glycolic acid) (PLGA) [109]. According to studies, resveratrol nanoparticles can help obese mice lose weight, adipose tissue mass, and inflammation. Resveratrol, a natural polyphenol found in certain plants like grapes and red wine, has garnered significant interest in the biomedical field due to its potential health-promoting properties. An innovative approach to harness the therapeutic potential of resveratrol is through the development of resveratrol nanoparticles. These nanoparticles are designed to encapsulate resveratrol within a carrier system, which can enhance its solubility, sustainable release, stability, and bioavailability (Fig. 4).

The study by Ahmad et al., involved the preparation of functional snacks enriched with nanoencapsulated resveratrol to assess their nutraceutical and physical properties. Nanoencapsulated resveratrol was derived from horse-chestnut (HRP), water-chestnut (WRP), and lotus-

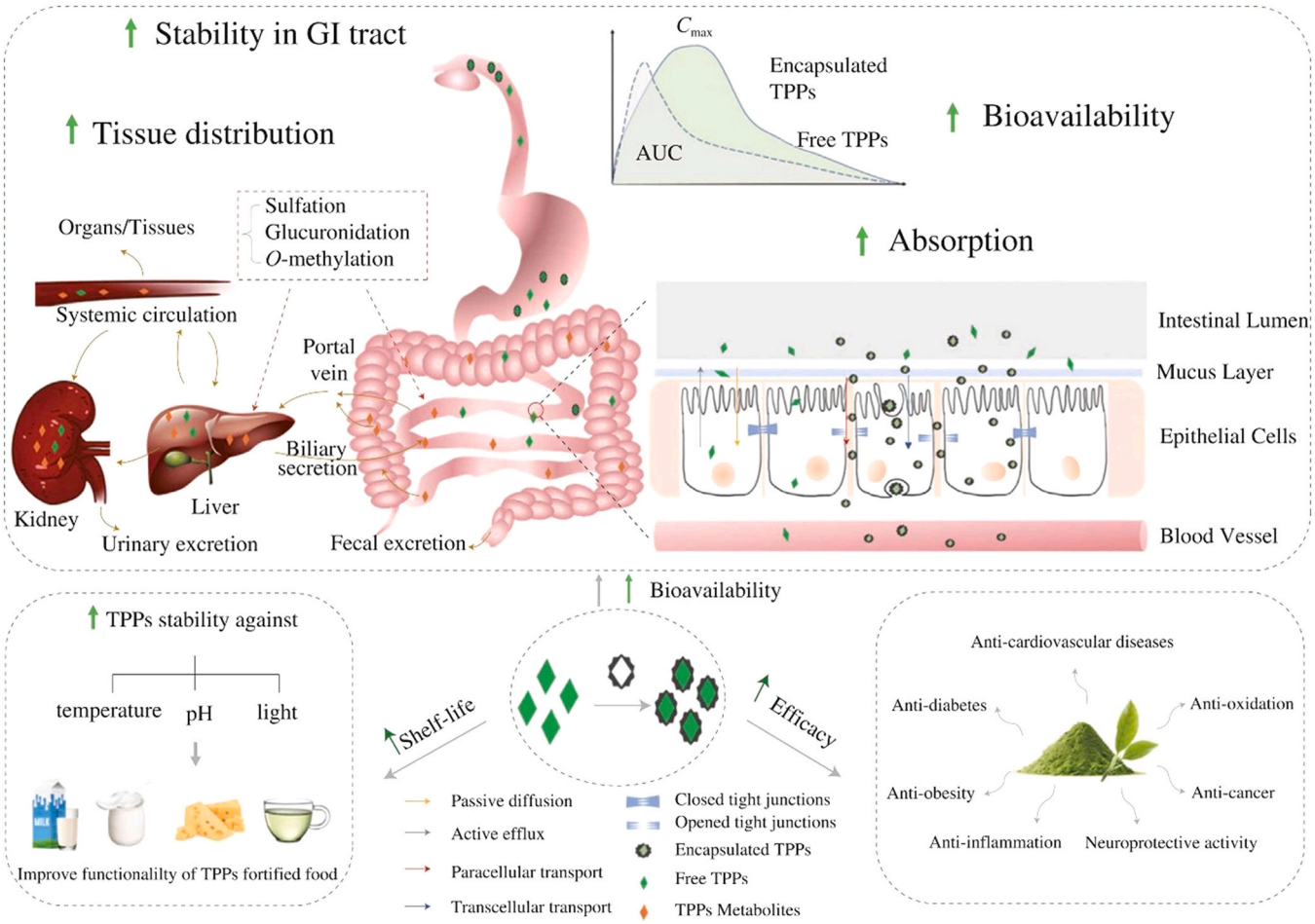

Fig. 4. Enhancing stability, bioavailability and bioefficacy of TPPs by encapsulations. The original image was adapted from [111], copyright 2022, elsevier.

stem starch particles (LRP), and was incorporated into wheat flour at a concentration of 0.4 % during the snack preparation process via extrusion. The snacks containing nanoencapsulated resveratrol exhibited notable antioxidant activity, ranging from 47 % to 61 %, as evidenced by their ability to inhibit lipid peroxidation. Additionally, they demonstrated antidiabetic effects, with inhibition percentages against α-glucosidase ranging from 23.23 % to 63.23 %. Furthermore, the snacks displayed anti-obesity properties, inhibiting pancreatic lipase activity by 24.86–44.46 % and cholesterol esterase activity by 59.58–74.1 %. The study underscored the importance of the encapsulation process in preserving the bioactivity of compounds during food processing, thereby preventing thermal degradation. It emphasized the significant nutraceutical potential of incorporating bioactive compounds in encapsulated form into various food formulations [110].

6.3. EGCG nanoliposomes

Green tea contains the polyphenol epigallocatechin-3-gallate (EGCG), which has anti-inflammatory and anti-obesity properties. According to studies, EGCG nanoliposomes can help obese mice lose weight while also reducing inflammation and the mass of their adipose tissue [111].

Epigallocatechin-3-gallate (EGCG), a potent polyphenol found in green tea, has gained attention for its potential health benefits, including antioxidant and anticancer properties. Researchers have explored the use of EGCG-loaded nanoliposomes to harness the therapeutic potential of EGCG in the biomedical field [112]. Nanoliposomes are nanoscale lipid-based vesicles that can encapsulate EGCG, improving its solubility and bioavailability. EGCG nanoliposomes have shown promise in various biomedical applications, including their use in cancer therapy, cardiovascular health, obesity and neuroprotection. The nano-sized liposomes offer advantages such as enhanced stability and controlled release, enabling targeted drug delivery and reducing potential side effects. Moreover, the formulation addresses the challenge of EGCG's poor bioavailability, making it a valuable tool for developing novel drug delivery systems and therapeutic strategies [112].

6.4. Quercetin-loaded nanoparticles

A flavonoid called quercetin, which is present in fruits and vegetables, has anti-inflammatory and anti-obesity properties. However, its insufficient bioavailability and poor solubility limit its efficacy. Utilizing polymeric substances like chitosan or PLGA, quercetin can be made into nanoparticles that increase its solubility and bioavailability. Quercetin-loaded nanoparticles have been proven to help obese mice lose weight, adipose tissue mass, and inflammation [54].

Quercetin, a natural flavonoid found in a variety of fruits and vegetables, has garnered interest in the biomedical field due to its potential health-promoting properties, including its antioxidant, anti-inflammatory, and anticancer effects [113]. To enhance the therapeutic potential of quercetin, researchers have explored the use of quercetin-loaded nanoparticles. These nanoparticles are designed to encapsulate quercetin, enhancing its solubility, stability, and bioavailability. In prospective research conducted by Dini et al., Quercetin-conjugated superparamagnetic iron oxide nanoparticles have been found to influence glucose metabolism-related genes and the miR-29 family in the hippocampus of rats. The study utilized quantitative polymerase chain reaction (qPCR) to assess the expression levels of

the miR-29 family, IGF-1, GLUT1, GLUT2, GLUT3, and GLUT4. Results indicate that diabetes leads to a significant upregulation of the miR-29 family and downregulation of GLUT1, GLUT2, GLUT3, GLUT4, and IGF-1 genes. Remarkably, treatment with QCSPIONs resulted in the reduction of miR-29 family expression while concurrently enhancing the expression of GLUT1, GLUT2, GLUT3, GLUT4, and IGF-1. In summary, the findings suggest that QCSPIONs may regulate the expression of the miR-29 family, thereby increasing the expression of glucose transporters and IGF-1, ultimately mitigating diabetic and possible obesity complications [114].

Quercetin-loaded nanoparticles have shown promise in a range of biomedical applications, including cancer therapy, cardiovascular health, and neuroprotection. The nano-sized particles offer several advantages, including improved drug release profiles and the ability to target specific tissues or cells, potentially reducing side effects. Furthermore, this approach addresses the challenge of quercetin's poor water solubility, making it a valuable tool for developing advanced drug delivery systems and therapeutic strategies [115].

6.5. Omega-3 fatty acid nanoparticles

The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have anti-inflammatory and anti-obesity properties. However, they are ineffective due to their poor solubility and low bioavailability. Since polymeric materials like PLGA improve the solubility and bioavailability of omega-3 fatty acids, they can be synthesized as nanoparticles. In obese mice, body weight, adipose tissue mass, and inflammation have been demonstrated to decrease in response to omega-3 fatty acid nanoparticle treatment [116].

Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have gained recognition for their potential health benefits, particularly in the context of obesity and related metabolic disorders. In biomedical applications, the development of omega-3 fatty acid nanoparticles holds great promise, especially in addressing obesity [117]. These nanoparticles are designed to encapsulate omega-3 fatty acids, improving their bioavailability and stability. Omega-3 fatty acid nanoparticles have shown potential as anti-obesity agents due to their ability to modulate various metabolic pathways, including inflammation, lipid metabolism, and appetite regulation. They can be used to enhance the effectiveness of weight management strategies, such as reducing body fat accumulation, improving insulin sensitivity, and alleviating obesity-related inflammation [118]. The nano formulation allows for controlled and sustained release of omega-3 fatty acids, optimizing their therapeutic impact. This approach contributes to the development of novel drug delivery systems and therapeutic strategies for combating obesity and related health issues [119].

6.6. Caffeine nanocapsules

The natural stimulant caffeine, which may be found in coffee and tea, has thermogenic and appetite-suppressing properties. The high doses needed for its anti-obesity benefits and harsh taste, however, limit its efficacy. Lipids or polymers can be used to shape caffeine into nanocapsules that will hide its bitter taste and increase its solubility and bioavailability. Caffeine nanocapsules have been shown in studies to help obese mice lose weight and fat mass [120].

Caffeine, a widely consumed natural stimulant, has drawn significant interest in the field of biomedicine, particularly for its potential as an anti-obesity agent. One innovative approach is the development of caffeine nanocapsules, which involve encapsulating caffeine within nano-sized lipid or polymer-based carriers. These nanocapsules aim to enhance the solubility, stability, and bioavailability of caffeine, making it a valuable tool in addressing obesity-related challenges [121]. Caffeine is known to stimulate thermogenesis, increase metabolic rate, and promote fat oxidation, making it a promising candidate for obesity management. Caffeine nanocapsules can offer controlled and sustained release, optimizing its anti-obesity effects. Additionally, the bitter taste and potential gastric irritation associated with caffeine consumption can be minimized by encapsulating caffeine within nanocarriers. This approach contributes to the development of novel drug delivery systems and therapeutic strategies for addressing obesity and related metabolic disorders [122].

6.7. Green tea polyphenol nanoparticles

Catechins and EGCG, two polyphenols found in green tea, have anti-inflammatory and anti-obesity properties. However, they are ineffective due to their poor solubility and low bioavailability. To increase the solubility and bioavailability of green tea polyphenols, they can be synthesized into nanoparticles utilizing polymeric substances like chitosan or PLGA. Green tea polyphenol nanoparticles have been proven in studies to help obese mice lose weight, adipose tissue mass, and inflammation [123].

Green tea polyphenols, particularly EGCG, have garnered significant attention for their potential health benefits, including their anti-obesity properties. In the realm of biomedicine, researchers have been exploring the application of green tea polyphenol nanoparticles, with a particular focus on combating obesity [111].

A study conducted by Zheng et al. focused on investigating the anti-obesity effect of (-)-epigallocatechin 3-O-(3-O-methyl) gallate (EGCG3″Me) when encapsulated in nanoparticles composed of chitosan (CS) and casein phosphopeptide (CPP). The EGCG3″Me-loaded chitosan-casein phosphopeptide (CS-CPP) nanoparticles were utilized for this purpose. Both EGCG3″Me and EGCG3″Me-loaded CS-CPP were found to influence the population of intestinal microbiota positively. They promoted the growth of specific beneficial bacteria while inhibiting the proliferation of *Bacteroides–Prevotella* and *Clostridium histolyticum*. Moreover, EGCG3″Me-loaded CS-CPP exhibited the most significant stimulatory effect on *Bifidobacterium* and *Lactobacillus–Enterococcus* spp. This underscores the efficacy of nanoparticle encapsulation in enhancing the bioactivity of EGCG3″Me, aiding in the prevention of obesity-related metabolic disorders [124].

Green tea polyphenol nanoparticles have demonstrated promise as anti-obesity agents due to their ability to modulate metabolic pathways, including increasing thermogenesis, improving lipid metabolism, and reducing adipogenesis. These nanoparticles can be used to enhance the efficacy of obesity management by promoting fat oxidation, suppressing appetite, and mitigating inflammation [125]. Their nano-sized formulation allows for improved absorption and controlled release of green tea polyphenols, optimizing their therapeutic impact. This innovative approach contributes to the development of novel drug delivery systems and therapeutic strategies for addressing the complex issue of obesity [126].

6.8. Fiber nanoparticles

Appetite suppression and satiety-inducing properties are provided by dietary fibers like psyllium and oat beta-glucan. However, their effectiveness is constrained by their poor solubility and bulky design [127]. Fibers can be transformed into nanoparticles by adopting techniques like electrospinning and spray drying, which reduce the size of the fibers and increase their solubility and bioavailability. Fiber nanoparticles have been demonstrated in studies to help obese mice lose weight and eat less food [128].

Fiber, particularly soluble dietary fiber, has found a compelling biomedical application, especially in the context of anti-obesity strategies. Researchers have been investigating the development of fiber nanoparticles to harness the health benefits of fiber in a more concentrated and targeted form. These nanoparticles are engineered to encapsulate soluble dietary fiber, enhancing its solubility and bioavailability. Fiber nanoparticles have shown promise in anti-obesity applications by virtue of their ability to promote satiety and reduce overall

caloric intake. Their nano-sized formulation allows for efficient delivery and dispersion within the gastrointestinal tract, where they can form gels and increase feelings of fullness, thereby suppressing appetite and supporting weight management [129]. Additionally, fiber nanoparticles can aid in stabilizing blood sugar levels, which is crucial for managing obesity and related metabolic disorders. This innovative approach contributes to the development of advanced drug delivery systems and therapeutic strategies for tackling obesity, offering a natural and safe means of supporting healthy weight control [130].

6.9. Conjugated linoleic acid (CLA) nanoemulsion

CLA is a fatty acid with anti-obesity properties that is present in dairy and meat products. However, its ineffectiveness is constrained by its poor solubility and low bioavailability. CLA can be created as a nanoemulsion, increasing its bioavailability and solubility. According to previous studies, CLA nanoemulsion can help obese mice lose weight, adipose tissue mass, and inflammation [131].

Conjugated linoleic acid (CLA) is a naturally occurring fatty acid with potential health benefits, particularly in the context of anti-obesity applications. In biomedicine, researchers have been exploring the use of CLA nanoemulsions to enhance the solubility and bioavailability of this compound, with a focus on combating obesity [132]. CLA nanoemulsions are engineered to encapsulate CLA, improving its dispersion in aqueous environments. These nano-sized emulsions have shown promise as anti-obesity agents due to their ability to influence fat metabolism and body composition. CLA is known for its potential to reduce body fat and increase lean body mass, making it a valuable candidate for obesity management. The nanoemulsion formulation enhances the stability and controlled release of CLA, optimizing its therapeutic potential [133]. Additionally, CLA nanoemulsions can minimize the typical issues associated with CLA supplementation, such as gastric discomfort. This innovative approach contributes to the development of advanced drug delivery systems and therapeutic strategies for addressing the multifaceted issue of obesity [134]. Fig. 5a provides an understanding of various nutraceuticals or nutrient-based nanoparticulate systems for the targeted delivery in obesity treatment.

7. Outlook and conclusion

The application of nutraceutical-based nanoparticles in the management of obesity offers substantial promise, primarily due to their capacity to enhance the solubility, stability, and bioavailability of bioactive compounds (Fig. 5b). These nanoparticles present a potential solution to several limitations associated with traditional obesity treatment approaches. However, the transition to their clinical application is not without its formidable challenges. Foremost among these challenges is ensuring the safety of nutraceutical-based nanoparticles, particularly due to risks such as bioaccumulation and organ toxicity. Comprehensive safety assessments, including longitudinal preclinical studies and biocompatibility testing, are imperative to thoroughly understand their potential cytotoxicity and adverse effects. Additionally, phased clinical trials and post-marketing surveillance must be prioritized to monitor chronic effects in humans. Gaining a comprehensive grasp of the toxicological aspects of these nanoparticles is essential for their responsible integration into clinical practice.

Regulatory frameworks must also evolve to address the unique challenges posed by nanomaterials, ensuring that safety standards are met before these technologies are widely adopted. Collaboration between researchers, regulatory bodies, and industry stakeholders is essential to develop guidelines that balance innovation with patient safety. The regulation of artificial intelligence as a medical device has highlighted some of the challenges of medical devices generally, and software as a medical device (SaMD) specifically, underscoring the need for robust regulatory oversight in emerging technologies. This necessitates the development of clear, evidence-based regulations that can adapt to the rapid advancements in nanotechnology while safeguarding public health.

In this modern era, it is imperative to prioritize the increased utilization of traditional herbal medicines and explore avenues for their seamless integration into a comprehensive public health framework. India, which is blessed with a rich diversity of medicinal plants in high demand across global markets, has begun tapping into this potential. To further this endeavor, there is a critical need to invest in research initiatives focused on natural products, agrotechnology, standardization, and quality control of herbal drugs. Scalable synthesis methods, such as microfluidics and green synthesis techniques using low-cost natural polymers like chitosan, can significantly reduce production costs. Understanding the socio-economic context and implementing policies conducive to research are essential steps toward fostering the sustainable development of this sector. Public-private partnerships and regulatory incentives for nanotechnology-based therapies can further enhance economic viability and accessibility. Long-term dietary flavonoid intake studies, for instance, highlight the importance of evaluating sustained effects and safety. Concurrently, efforts aimed at conserving the biodiversity of medicinal plants and combating biopiracy are crucial for sustaining the growth trajectory of the industry. Presently, there exists a timely opportunity to systematically compile and document traditional knowledge pertaining to our invaluable plant resources. Moreover, substantiating their efficacy through meticulous phytochemical, biological, and pharmacological investigations will be instrumental in validating their potential benefits and ensuring their acceptance within modern healthcare frameworks.

Furthermore, the integration of nanotechnology into obesity treatment introduces critical pharmacokinetic considerations. Understanding how these nanoparticles may modify the absorption, distribution, metabolism, and excretion (ADME) of encapsulated compounds is a priority. Research efforts must focus on elucidating these alterations and their implications for treatment effectiveness. Regulatory frameworks must also evolve to address the unique challenges posed by nanomaterials, ensuring that safety standards are met before these technologies are widely adopted. Collaboration between researchers, regulatory bodies, and industry stakeholders is essential to develop guidelines that balance innovation with patient safety.

In addition, the cost-effectiveness of incorporating nanotechnology into obesity management is a central concern. Strategies such as optimizing nanoparticle synthesis using scalable and cost-effective methods (e.g., wire-assisted or laser-assisted techniques) and leveraging natural polymers can streamline production processes. Continual progress in the realm of nanomedicine and nanotechnology holds exciting prospects for improving the delivery and efficacy of nutraceutical-based treatments for obesity. Synergistic approaches combining nanoparticles with lifestyle interventions or pharmaceutical drugs should also be explored to enhance personalized treatment strategies.

To comprehensively grasp the sustained effects and safety of nutraceutical-based nanoparticles in obesity treatment, long-term studies must evaluate both durability of treatment effects and potential risks such as immune responses or unintended metabolic disruptions. Post-marketing surveillance will be critical to monitor real-world outcomes and ensure patient safety. Ultimately, the translation of nutraceutical-based nanoparticle research into clinical practice necessitates robust scientific evidence. Well-designed clinical trials play a pivotal role in validating the efficacy and safety of these approaches in real-world applications. In the realm of obesity management, a multitude of challenges must be addressed, including the need for personalized treatment approaches, patient compliance, and addressing the multifaceted nature of obesity. Nanotechnology offers an innovative pathway to confront these challenges. By optimizing the production and delivery of nutraceutical-based nanoparticles, cost-effectiveness can be improved, making these treatments more accessible. Moreover, combining these nanoparticles with other modalities and conducting long-term studies will enhance their overall effectiveness and safety. In

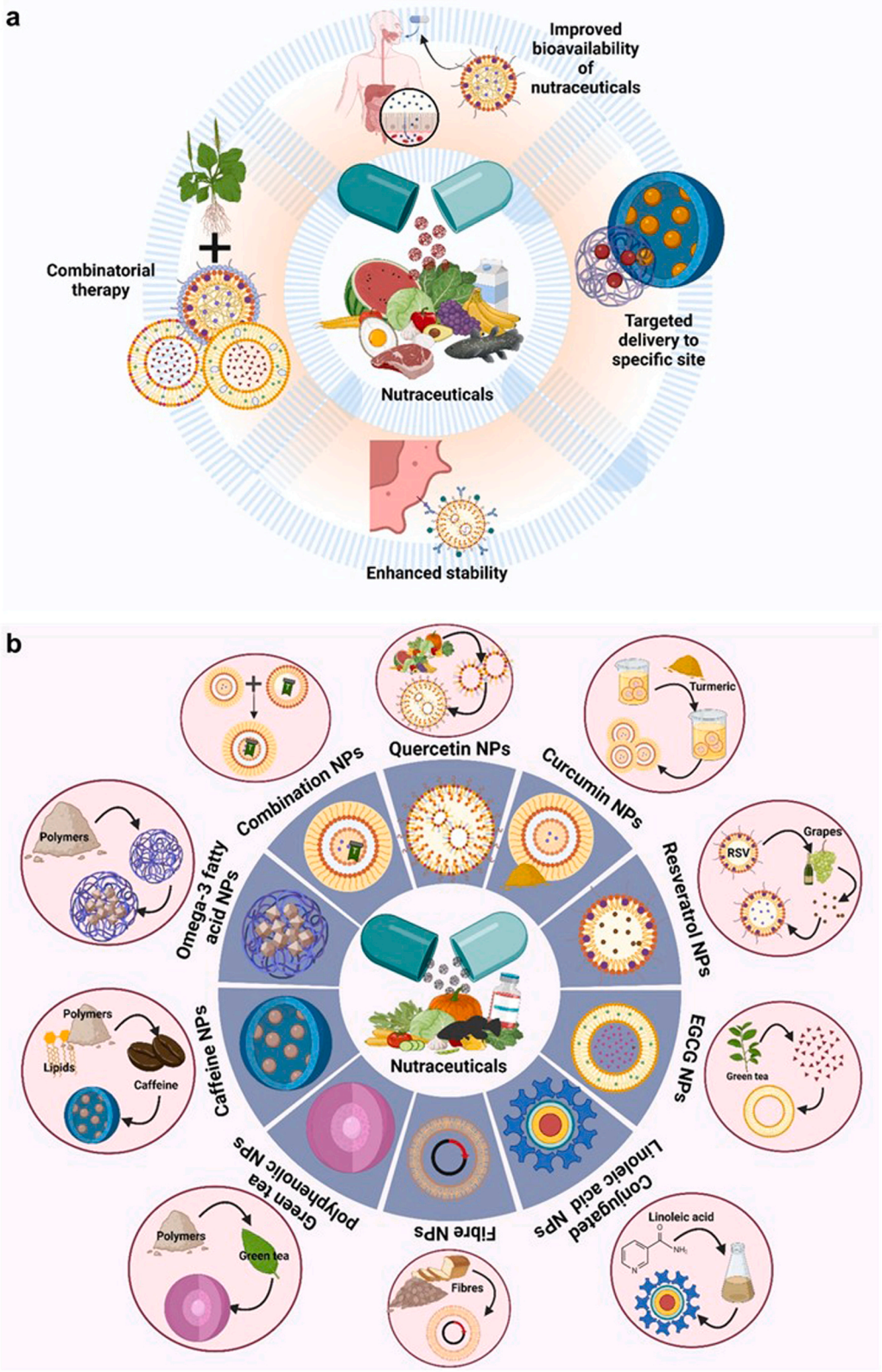

Fig. 5. A. Graphical summarization of potential applications of nutraceuticals and improvement of their biological activity via combinatorial therapy, I.e., nanoparticles for targeted or site-specific delivery. B. possibilities of various nutraceuticals or nutrient-based nanoparticulate systems for the targeted delivery in obesity treatment (*created with biorender.com*).

essence, the future of obesity management lies at the intersection of nanotechnology and tailored evidence-based approaches.

CRediT authorship contribution statement

Sagnik Nag: Writing – original draft. **Johan Sukweenadhi:** Writing – original draft, Supervision, Conceptualization. **Sourav Mohanto:** Writing – original draft. **Haribalan Perumalsamy:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Deong Hwan Oh:** Writing – review & editing. **Md Amdadul Huq:** Supervision, Conceptualization. **Sumathi Sundaravadivelu:** Writing – original draft. **Selvakumar Vijayalakshmi:** Writing – original draft. **Sri Renukadevi Balusamy:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.procbio.2025.05.021.

Data availability

Data will be made available on request.

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