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AI-ASSISTED DRUG DISCOVERY OF WEIGHT MANAGEMENT AGENTS: ORLISTAT, SEMAGLUTIDE, AND NATURAL PRODUCTS *GARCINIA CAMBOGIA* AND GLUCOMANNAN

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ABSTRACT

Obesity is a major public health issue worldwide and is a major risk factor for type 2 diabetes, cardiovascular diseases, and metabolic syndrome. Obesity management includes pharmacological interventions, natural products, and lifestyle changes. This study comprehensively evaluates two of the most popular anti-obesity drugs, Orlistat and Semaglutide, and the natural products *Garcinia cambogia* and Glucomannan. Scientific literature suggests that Orlistat is a potent anti-obesity agent that decreases body weight, BMI, and waist circumference by inhibiting gastrointestinal lipases and limiting the absorption of dietary fats. Semaglutide, a glucagon-like peptide-1 receptor agonist, induces weight loss through mechanisms that involve appetite reduction, delayed gastric emptying, and insulin secretion enhancement. *Garcinia cambogia*, with high hydroxycitric acid content, may inhibit lipogenesis and influence appetite control through central nervous system-mediated neurotransmitter action, whereas Glucomannan, a soluble dietary fiber, may increase feelings of fullness and lower caloric intake through gel formation in the GI tract. *In silico* pharmacokinetic and pharmacodynamic studies indicated that Orlistat and Glucomannan have good safety profiles; however, the activity of Semaglutide could not be predicted due to its peptide nature. Predictions for biological activity indicated that the natural compounds may have anti-obesity, lipid-lowering, and anti-diabetic activities. Overall, clinical and computational studies demonstrate the relative effectiveness, mechanisms of action, and safety profiles of synthetic drugs and herbal supplements for weight loss. This is especially useful for clinicians, researchers, and individuals seeking evidence-based approaches to managing obesity. Further studies are necessary to assess safety and determine optimal dosage regimens for pharmacological and herbal agents for weight loss.

Keywords: Obesity, Orlistat, Semaglutide, *Garcinia cambogia*, Glucomannan, *In Silico* Analysis, Weight Management, Pharmacokinetics, Pharmacodynamics

INTRODUCTION

The medical condition known as obesity develops when body fat exceeds normal levels, leading to multiple health problems. It is commonly identified using body mass index (BMI), where a value of 30 kg/m² or higher defines obesity in adults[1]. Obesity results from multiple factors, including regular consumption of high-calorie processed foods, lack of physical activity, genetic conditions, and environmental changes associated with modern lifestyle. Worldwide obesity has been rising rapidly, affecting both developed and developing countries and placing increasing demands on public health systems[2]. There are findings that indicate that in 2021, 2.11 billion adults aged 25 and older were overweight or obese, representing 45% of the global adult population. Women were affected more frequently than men, with 1.11 billion women compared to 1.00 billion men having the condition. Eight countries, including China, India, the United States, Brazil, Russia, Mexico, Indonesia, and Egypt, now have more than half of all global overweight and obesity cases. The Middle East and North Africa (MENA) region shows through its research that obesity prevalence among children and teenagers in this area keeps rising at a fast pace, reaching 49.4% in specific countries[3]. Research conducted with United Arab Emirates population data showed that 62% of adults had overweight or obesity conditions, which proved obesity has become a major national public health concern[4]. Overall, the rising number of overweight and obese people has developed into a significant public health issue because their weight status creates elevated risks for developing type 2 diabetes and cardiovascular disease[2].

Medication and Herbs for Obesity

Various interventions can be used to manage weight, such as medications and herbs/natural supplements. Orlistat and Semaglutide are two of the medications that are commonly used. *Garcinia cambogia* and Glucomannan are the most frequently used herbs.

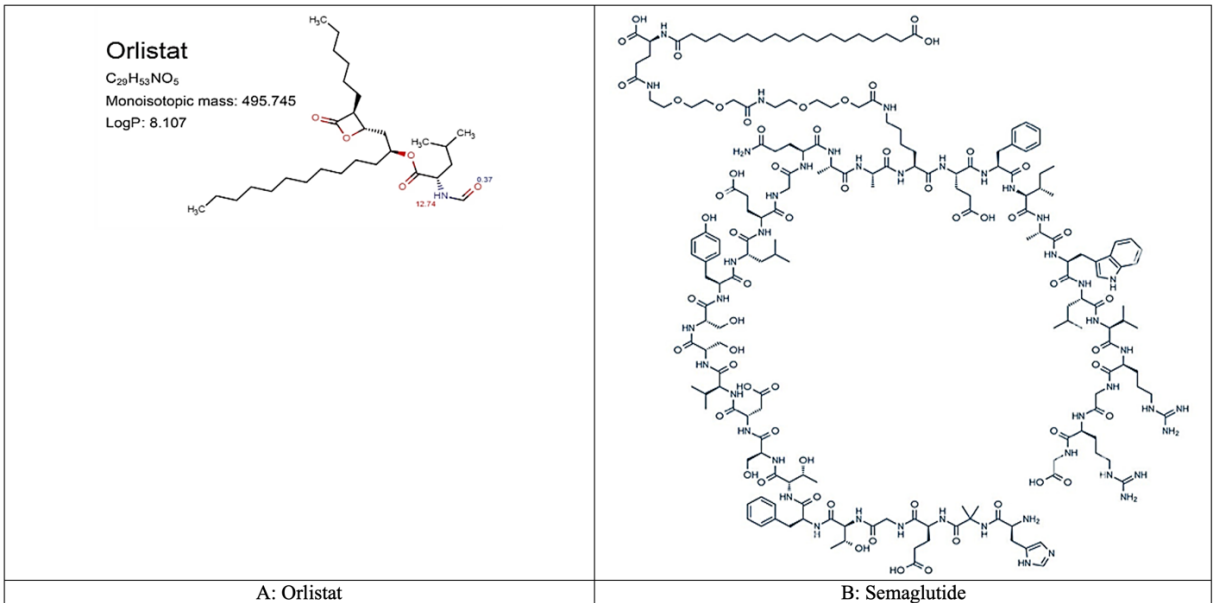
Orlistat (Xenical®) is a novel non-centrally acting anti-obesity agent that acts locally in the gastrointestinal tract to inhibit pancreatic and gastric lipases, enzymes that play a crucial role in the digestion of long-chain triglycerides [5]. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by about 30%[5]. *Orlistat* is approved for treatment of obese patients with body mass index ≥30 kg/m² or overweight patients (BMI ≥28 kg/m²) with risk factors such as diabetes or hypertension[5]. Regarding its mechanism of action, Orlistat is a chemically synthesised hydrogenated derivative of lipstatin, a naturally occurring lipase inhibitor produced by *Streptomyces toxytricini*[6]. *Orlistat* exerts its therapeutic activity in the lumen of the gastrointestinal tract by forming a covalent bond with the active site serine residue of gastric and pancreatic lipase. The inactivated enzymes are unable to hydrolyse dietary fat in the form of triglycerides to absorbable free fatty acids and monoglycerides[5]. This causes about 30 percent of the fat taken in to be excreted undigested, resulting in a decrease in caloric absorption, and loss of weight when used with a hypocaloric diet[6]. So, orlistat is a highly effective drug to use for weight loss and has fewer adverse effects. It generally has a good safety profile, and most adverse effects are mild

gastrointestinal symptoms, with low systemic toxicity because its action is limited to the gastrointestinal tract[7]. (Figure 1)

Semaglutide is a second-generation medication according to Ryan, 2021[8], which has attracted a lot of attention in the treatment of obesity. It is an analogue of the naturally occurring hormone glucagon-like peptide-1 (GLP-1) and is about 94 per cent similar to the original peptide structure. Small structural changes enhance stability and extend its duration of action in the body. Whereas natural GLP-1 is active only for 1-2 minutes, semaglutide has a longer half-life of approximately 165 hours, enabling it to be used as a convenient single-dose weekly subcutaneous injection. Semaglutide is used to treat obesity with a dose of 2.4 mg/week. By contrast, 0.5 mg and 1.0 mg weekly doses are authorised for type 2 diabetes. The higher dose of 2.4 mg was chosen to help people achieve significant, lasting weight loss. Semaglutide is an important evolution in the contemporary pharmacological response to obesity because of its long-term activity and specific focus. Semaglutide works by activating GLP-1 receptors that are primarily located in the pancreas, gut, and the brain. On stimulation of these receptors, semaglutide boosts glucose-dependent insulin secretion, implying that the release of insulin rises when the glucose in the blood increases following the consumption of food[9]. Simultaneously, it decreases the secretion of glucagon and decreases the rate of gastric emptying, which are co-beneficial in reducing the levels of blood glucose[9]. Semaglutide is also known to affect the level of appetite since it targets receptors in the hypothalamus, which reduce the amount of hunger, the number of food cravings, and the level of fullness[9]. The overall effects of these are better glycemic management, as well as considerable weight loss[9].

In the case of the herb *Garcinia cambogia*, a tropical fruit with high hydroxycitric acid (HCA) content, biochemical effects on metabolic mechanisms that control weight have been widely studied[10]. Regarding mechanism of action, early biochemical and animal work suggested that HCA is a strong inhibitor of the cytosolic enzyme, ATP citrate lyase, which transforms citrate into acetyl CoA, a precursor of fatty acids and cholesterol formation; inhibiting this process suppresses lipogenesis and instead induces the use of carbohydrates to store as glycogen instead of making them fat[10]. Other mechanistic studies indicated that HCA has the capacity to affect central appetite circuits by altering the levels of serotonin, and this could be related to suppressed food consumption in experimental animals[11]. Its efficacy is still unstable, and Safety issues have begun to take more centre stage, especially the association of Garcinia-containing supplements being hepatotoxic with hundreds of cases of acute liver injury[12]. (Figure 2)

According to Keithley *et al*., 2013 [13] glucomannan is a dietary fibre present in water, has been extracted and used in traditional Asian cuisine, and is currently sold as a dietary supplement to treat all sorts of ailments. It is a high-molecular-weight polysaccharide containing beta-1,4-linked D-glucose and D-mannose, and it can absorb up to 50 times its weight in water, forming a viscous gel in the gastrointestinal tract. This gel coating slows gastric emptying, creates a sense of fullness, and may also help reduce food intake to support weight loss; it can also disrupt micelle formation to reduce cholesterol uptake and slow intestinal glucose absorption to improve glycemic control in type 2 diabetes. To be used therapeutically, glucomannan is usually given in divided doses before meals in a sufficient amount of water to avoid gastrointestinal obstruction and should also not be mixed with drugs to avoid interference with drug absorption. Its therapeutic uses would encompass weight control, the enhancement of glycemic control, reduction of cholesterol, and the treatment of constipation, metabolic syndrome, and as a food additive to enhance texture and augment the presence of fibers. Most researchers state that the safety profile at this dosage is reasonable, and most adverse effects are minor and gastrointestinal, including abdominal bloating, gas, diarrhoea, constipation, and discomfort[14]. Moreover, severe side effects are rare and are usually corrected by reducing the dose or increasing fluid intake.



A: Orlistat | B: Semaglutide

Figure 1: The Chemical Structure of the Used Drugs, A: Orlistat, and B: Semaglutide

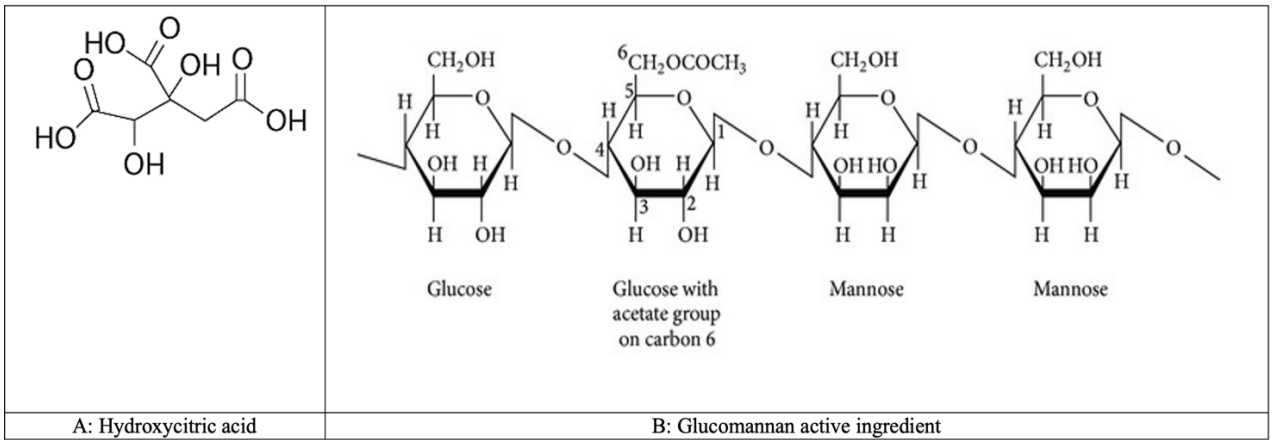


Figure 2: The Chemical Structure of the herbs A: Hydroxycitric acid, the active ingredient of *Garcinia cambogia*, and B: Glucomannan, the active ingredient

MATERIALS AND METHODS

This study aimed to conduct a literature review and *in silico* assessment of the chosen anti-obesity drugs, i.e., Orlistat, Semaglutide, *Garcinia cambogia*, and Glucomannan.

Literature Search and Study Selection

We systematically searched PubMed, Google Scholar, PubChem, and relevant academic book chapters to identify scientific sources. Search terms consisted of the names of the chosen drugs and natural products, along with the names of obesity, overweight, body weight, body mass index (BMI), waist circumference, appetite control and weight loss. We also reviewed the reference lists of relevant publications to identify additional eligible studies. The focus was on peer-reviewed human clinical studies, and no publication date restriction was applied to maximise coverage.

Inclusion and Exclusion Criteria

Inclusion criteria

- Studies involving overweight or obese human participants.
- Studies evaluating Orlistat, Semaglutide*, Garcinia cambogia,* or Glucomannan.
- Studies reporting weight-related outcomes such as body weight, BMI, waist circumference, fat mass, or appetite-related measures.
- Randomised controlled trials, observational studies, and systematic reviews.

Exclusion criteria

- Studies primarily focused on other medical conditions (e.g., diabetes or cardiovascular disorders) unless weight outcomes were reported.
- Studies lacking relevant anthropometric or metabolic data.
- Animal or *in vitro* studies, except when used to explain mechanisms of action.
- Non-peer-reviewed materials, except when necessary for general background information.

In Silico Analysis

The pharmacokinetic properties, biological activity, and safety profiles of the chosen compounds were predicted using computer-based prediction tools. We obtained the chemical structures and SMILES of orlistat, semaglutide, constituents of *Garcinia cambogia,* and glucomannan-related compounds from PubChem, which served as input for the analysis. SwissADME was used to evaluate physicochemical properties and pharmacokinetic properties such as molecular weight, lipophilicity (logP), water solubility, gastrointestinal absorption, blood-brain barrier permeability, cytochrome P450, P-glycoprotein substrate, bioavailability score, and drug-likeness rules. We estimated acute oral toxicity (LD 50), toxicity classifications, and possible organ-specific toxicity (hepatotoxicity, nephrotoxicity, cardiotoxicity, neurotoxicity, and respiratory toxicity) using ProTox-II. We used Way2Drug (PASS online) to predict potential biological activities and the most likely molecular targets based on structural characteristics. The probability of activity (Pa) values was compared in order to determine high-confidence predicted pharmacological effects. *In silico* divergent results were combined with clinical results to guide the interpretation of the efficacy and safety profiles of each anti-obesity agent.

Data Organisation and Analysis

We systematically tabulated the clinical study and *in silico* prediction data for comparison. We summarised clinical outcomes (e.g., change in body weight, BMI, and waist circumference), along with predicted pharmacokinetic and safety parameters. We compared pharmacological (orlistat and semaglutide) and herbal products (*Garcinia cambogia* and glucomannan) to identify similarities and differences in efficacy, mechanism of action, pharmacokinetics, and safety profiles. Findings were interpreted through narrative synthesis and indicated therapeutic potential and safety considerations.

In Vivo (Clinical) Investigation of Orlistat and Semaglutide

Tables 1- 4.

In Vivo (Clinical) Investigation of *Garcinia cambogia* and Glucomannan

Tables 5- 8.

Table 1: Clinical studies of Orlistat (Safety)

Author	Acharya *et al*., 2006 [15]	Jain *et al*., 2011 [16]	Guy-Grand *et al*., 2004 [17]
Study Design	Multicentre RCT	Randomized, single-blind	Randomized, double-blind RCT
Study Duration	12 months	24 weeks	6 months
Gastrointestinal Events	Common (steatorrhea, oily stools)	Reported	Common
Diarrhea	Frequently reported	Reported	Frequently reported
Liver Enzymes (ALT/AST)	Not significantly elevated	Monitored; no major change	No major safety concern reported
Fat-Soluble Vitamins	Vitamin E and β-carotene reduced	Not specified	Not specified
Serious Adverse Events	Rare	Rare	Rare
Discontinuation Due to AEs	Some due to GI effects	Limited	Limited
Overall Tolerability	Generally, well tolerated	Well tolerated	Well tolerated

Table 2: Clinical studies of Orlistat (Efficacy)

Author	Acharya *et al*., 2006 [15]	Jain *et al*., 2011 [16]	Guy-Grand *et al*., 2004 [17]
Study Design	Multicentre, randomized, double-blind, placebo-controlled	Prospective, randomized, single-blind	Randomized, double-blind, placebo-controlled
Participants	228 obese adults	80 obese adults	1,004 overweight/obese patients with comorbidities
Study Duration	12 months	24 weeks	6 months
Medication	Orlistat 120 mg TID	Orlistat 120 mg TID	Orlistat 120 mg TID
Body Weight (Before → After)	~97 kg → ~88.8 kg vs ~91.8 kg (placebo)	80.2 kg → 75.55 kg vs 79.8 kg → 77.3 kg (placebo)	92.5 kg → 88.7 kg vs 92.8 kg → 91.5 kg (placebo)
≥5% Weight Loss	Higher vs placebo ($P < 0.05$)	Significant vs placebo	Significant vs placebo
≥10% Weight Loss	Higher vs placebo	Not specified	Moderate proportion achieved
BMI Change	Reduced	29.6 → 27.7 (↓ 6.5%)	Reduced
Waist Circumference	Reduced	102.3 cm → 97.5 cm (↓ 4.8%)	Reduced
LDL-Cholesterol	Significantly reduced	Reduced	145 → 128 mg/dL (↓ 11.7%)
Glycemic Control (HbA1c)	Not primary outcome	Not measured	8.1% → 7.56% (↓ 0.54%)

Table 3: Clinical Studies of Semaglutide (Safety)

Author	Wilding *et al*., 2021 [18]	Wadden *et al*., 2021 [19]	Rubino *et al*., 2021 [20]
Study Design	STEP 1: Standard lifestyle intervention	STEP 3: Intensive behavioral therapy (30 visits, 8-week low-calorie diet)	STEP 4: Withdrawal design for long-term use
Location / Participants	16 countries / 5 continents / 1,961 adults with obesity	41 USA sites / 611 adults with obesity	10 countries / 4 continents / 902 adults with obesity
Patient Demographics	Mean Age 46 / 74% female / BMI 37.9	Mean Age 46 / 81% female / BMI 38.0	Mean Age 46 / 81% female / BMI 38.0
Study Duration	68 weeks	68 weeks	68 weeks (20 weeks run-in + 48 weeks randomized)
Nausea	44% vs. 17%	Not specified	~35% vs. ~12%
Vomiting	25% vs. 7%	Not specified	~17% vs. ~4%
Diarrhea	32% vs. 16%	Not specified	~25% vs. ~12%
Constipation	23% vs. 10%	Not specified	Not specified
Discontinuation Due to Adverse Events	7.0% vs. 3.1%	5.9% vs. 2.9%	2.4% vs. 2.2% (after initial period)
Acute Pancreatitis	0.2% (3 cases) vs. 0%	Not specified	0.2% vs. 0.3%
Malignant Neoplasms	1.1% vs. 1.1%	Not specified	1.1% vs. 0.4%
Deaths	0.2% vs. 0.3%	Not reported	Not reported
Hypoglycemia	0.6% vs. 0.8%	Not specified	Not specified
Injection-Site Reactions	5.0% vs. 6.7%	Not specified	Not specified

Table 4: Clinical Studies of Semaglutide (Efficacy)

Author	Wilding *et al*., 2021 [18]	Wadden *et al*., 2021 [19]	Rubino *et al*., 2021 [20]
Study Design	STEP 1: Standard lifestyle intervention	STEP 3: Intensive behavioral therapy (30 visits, 8-week low-calorie diet)	STEP 4: Withdrawal design for long-term use
Location / Participants	16 countries / 1,961 adults with obesity	41 USA sites / 611 adults with obesity	10 countries / 902 adults with obesity
Patient Demographics	Mean Age 46 / 74% female / BMI 37.9	Mean Age 46 / 81% female / BMI 38.0	Mean Age 46 / 81% female / BMI 38.0
Study Duration	68 weeks	68 weeks	68 weeks (20 weeks run-in + 48 weeks randomized)
≥5% weight loss	86.4% vs. 31.5%	86.6% vs. 47.6%	88.7% from week 0 vs. 46.6% from week 0
≥10% weight loss	69.1% vs. 12.0%	75.3% vs. 26.6%	Not specified
≥15% weight loss	50.5% vs. 4.9%	56.7% vs. 13.7%	Not specified
≥20% weight loss	32.0% vs. 1.7%	Not specified	Not specified
Waist Circumference Change	-13.5 cm vs. -4.1 cm	Not specified	Not specified
Systolic Blood Pressure Change	-6.2 mmHg vs. -1.1 mmHg	Not specified	Not specified

Patients Achieving Normoglycemia	84% vs. 47% (from prediabetes)	Not specified	Not specified
Physical Function Improvement	Significant improvement vs. placebo	Not specified	Not specified
Treatment Adherence	81.1%	82.7%	92.3% of randomized patients

Table 5: Clinical studies of *Garcinia cambogia* (Efficacy)

Author	Hayamizu *et al*., 2003 [21]	Acharya *et al*., 2006 [15]; Maia-Landim *et al.,* 2018 [22]	Heymsfield *et al*., 1998 [23]
Study Design	Randomized, double-blind, placebo-controlled	Prospective clinical intervention	Randomized, double-blind, placebo-controlled
Participants	44 adults with high visceral fat	214 overweight/obese adults	135 overweight adults
Study Duration	12 weeks (+ 4-week follow-up)	6 months	12 weeks
Medication	Garcinia extract (~1000 mg HCA/day)	Garcinia + Glucomannan (500 mg twice daily each)	Garcinia extract (1500 mg HCA/day)
Body Weight (Before → After)	Minimal change	~92.4 kg → ~85.3 kg	~92.1 kg → ~88.9 kg vs ~92.3 kg → ~88.2 kg (placebo)
≥5% Weight Loss	Not significant	Achieved in substantial proportion	Not superior to placebo
≥10% Weight Loss	Not reported	Observed in some participants	Not significant
Visceral Fat	131 → 114 cm² (↓ ≈13%) vs placebo minimal change	Significantly reduced	Not primary endpoint
Fat Mass	Reduced	Significantly reduced	Reduced but not significant vs placebo
Lipid Profile	Not primary outcome	Cholesterol decreased	Not significant
Fasting Glucose	Not reported	Decreased	Not significant

Table 6: Clinical studies of *Garcinia cambogia* (Safety)

Author	Hayamizu *et al*., 2003 [21]	Acharya *et al*., 2006 [15]; Maia-Landim *et al.,* 2018 [22]	Heymsfield *et al*., 1998 [23]
Study Design	Randomized, double-blind RCT	Prospective clinical intervention	Randomized, double-blind RCT
Study Duration	12 weeks	6 months	12 weeks
Adverse Events	No serious events reported	No serious adverse effects reported	No significant adverse events
Gastrointestinal Effects	Mild, infrequent	Mild	Mild
Laboratory Monitoring	Clinical observation only	Clinical monitoring performed	Clinical labs assessed
Serious Adverse Events	None reported	None reported	None reported
Discontinuation Due to AEs	Not significant	Not significant	Not significant
Overall Tolerability	Well tolerated	Well tolerated	Well tolerated

Table 7: Clinical Studies of Glucomanann (Safety)

Author	Walsh *et al.,* 1984 [24]	Keithley *et al.,* 2013 [13]	Birketvedt *et al.,* 2005 [25]
Study Type	Randomized, double-blind, placebo-controlled trial	Randomized, double-blind, placebo-controlled trial	Randomized, double-blind, placebo-controlled trial
Study Population	20 obese subjects	53 overweight and moderately obese adults	176 overweight and obese adults
Mean Age	Not specified	40.6 years	Not specified
Gender	Not specified	~85% female	Not specified
Mean BMI (kg/m²)	Not specified	~31	Not specified
Intervention	Glucomannan 1 g three times daily (3 g/day)	Glucomannan 1.33 g three times daily (3.99 g/day)	Glucomannan plus fiber blend
Study Duration	8 weeks	8 weeks	5 weeks
Gastrointestinal Symptoms	No adverse reactions reported	Transient bloating, eructation (burping), fullness (resolved in 1-3 days)	Not specified
Discontinuation Due to AEs	None	None (3 lost to follow-up per group for personal reasons)	Not specified
Hepatic/Renal Safety	Not assessed	Liver enzymes and creatinine remained normal	Not assessed
Deaths	None	None	None

Table 8: Clinical Studies of Glucomannan (Efficacy)

Author	Walsh *et al.,* 1984 [24]	Keithley *et al.,* 2013 [13]	Birketvedt *et al.,* 2005 [25]
Study Type	Randomized, double-blind, placebo-controlled trial	Randomized, double-blind, placebo-controlled trial	Randomized, double-blind, placebo-controlled trial
Study Population	20 obese subjects	53 overweight and moderately obese adults	176 overweight and obese adults
Mean Age	Not specified	40.6 years	Not specified
Gender	Not specified	~85% female	Not specified
Mean BMI (kg/m²)	Not specified	~31	Not specified
Intervention	Glucomannan 1 g three times daily (3 g/day)	Glucomannan 1.33 g three times daily (3.99 g/day)	Glucomannan plus fiber blend
Study Duration	8 weeks	8 weeks	5 weeks
Mean Weight Loss	-5.5 lbs (significant) vs. placebo	-0.40 kg vs. -0.43 kg (not significant)	Significant weight loss in fiber groups

Waist Circumference	Not assessed	Not assessed	Not assessed
Total Cholesterol	-21.7 mg/dL (significant)	No significant change	Not specified
LDL Cholesterol	-15.0 mg/dL (significant)	No significant change	Not specified
HDL Cholesterol	Not significant	No significant change	Not specified
Triglycerides	Not significant	No significant change	Not specified
Satiety/Hunger Scores	Not assessed	No significant change	Not specified
Body Composition Change	Not assessed	No significant change	Not specified

Table 9: Pharmacokinetics of Orlistat, Semaglutide, *Garcinia cambogia,* and Glcomannan

Properties	Parameters	Orlistat	Semaglutide	*Garcinia cambogia*	Glucomannan
Physicochemical Properties	MW (g/mol)	495.73 g/mol	None	406.70 g/mol	666.58 g/mol
	HBA	5	None	4	21
	HBD	1	None	2	14
Lipophilicity Log Po/w	ILOGP	5.46	None	3.03	-0.83
	XLOGP3	9.96	None	3.84	-9.02
	MLOGP	4.66	None	2.79	-8.02
Solubility	Class	Poorly Soluble	None	Moderately Soluble	Highly Soluble
Absorption	GI	Low	None	High	Low
	LOG KP Skin Permeation cm/s	-2.25 cm/s	None	-6.05 cm/s	-16.77 cm/s
	Bioavailability Score	0.55	None	0.55	0.17
Distribution	BBB permeant	No	None	YES	NO
Metabolism	CYP1A2 inhibitor	No	None	NO	NO
	CYP2C19 inhibitor	No	None	NO	NO
	CYP2C9 inhibitor	Yes	None	NO	NO
	CYP2D6 inhibitor	No	None	NO	NO
	CYP3A4 inhibitor	No	None	NO	YES
Lipinski's rule		Yes; 1 Violation:MLOGP>4.15	None	Yes, 0 Violation	Not Obeyed

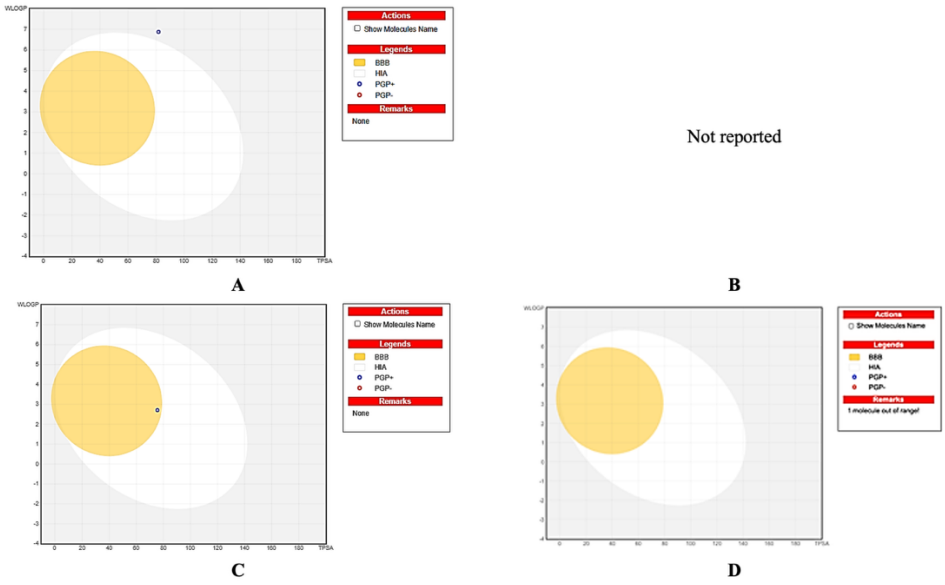
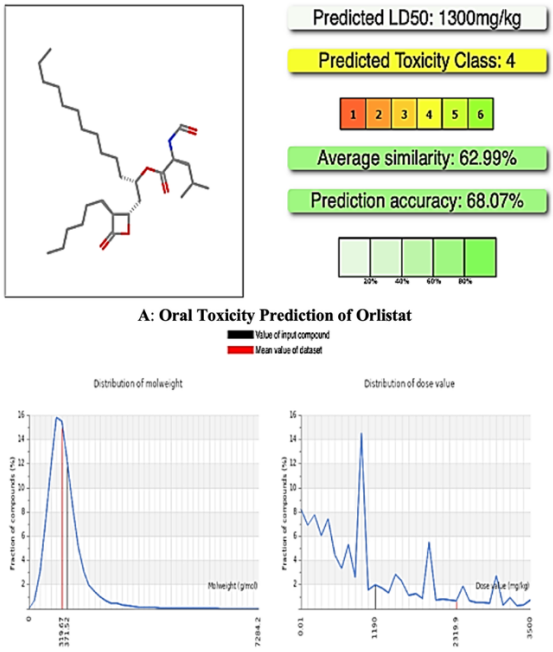


Figure 3: Boiled egg model of A) Orlistat, B) Semaglutide, C) *Garcinia cambogia*, and D) Glucomannan

Table 10: Pharmacodynamics

Target	Class	Orlistat	Semaglutide	*Garcinia cambogia*	Glucomannan
Vascular endothelial growth factor A	Secreted protein	-	-	-	0.179283316959
Acidic fibroblast growth factor	Secreted protein	-	-	-	0.179283316959
Basic fibroblast growth factor	Secreted protein	-	-	-	0.179283316959
Heparanase	Enzyme	-	-	-	0.179283316959
Cyclin-dependent kinase 1	Kinase	-	-	-	0.131843613207
Galectin-4	Other cytosolic protein	-	-	-	0.0842079066169
Galectin-8	Other cytosolic protein	-	-	-	0.0842079066169
Monoacylglycerol lipase ABHD6	Enzyme	1.0	-	-	-
Cannabinoid receptor 1	Family A G protein-coupled receptor	1.0	-	-	-
LDL-associated phospholipase A2	Enzyme	1.0	-	-	-
Monoacylglycerol lipase ABHD12	Enzyme	1.0	-	-	-

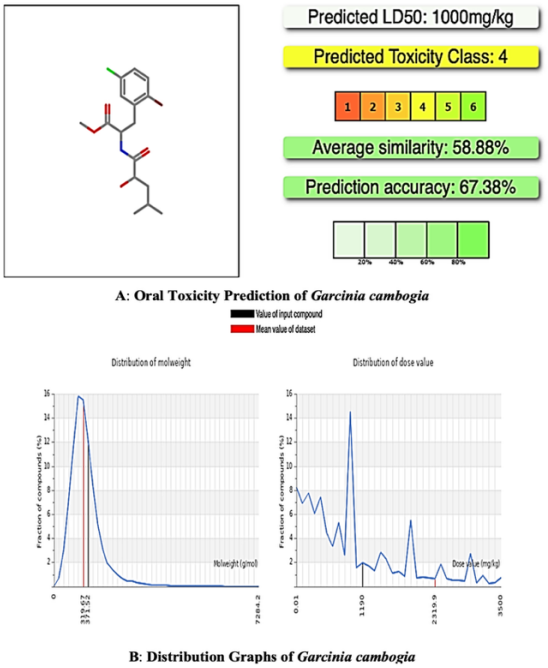
Sn1-specific diacylglycerol lipase beta	Enzyme	1.0	-	-	-
Sn1-specific diacylglycerol lipase alpha	Enzyme	1.0	-	-	-
Protein BAT5	Enzyme	1.0	-	-	-
Histone deacetylase 6 (HDAC6)	Eraser	-	-	0.109945769839	-
Histone deacetylase 1 (HDAC1)	Eraser	-	-	0.109945769839	-
Androgen Receptor (AR)	Nuclear receptor	-	-	0.101613854776	-
P-glycoprotein 1 (ABCB1)	Primary active transporter	-	-	0.101613854776	-
Sulfonylurea receptor 2 (ABCC9)	Primary active transporter	-	-	0.101613854776	-
Phosphodiesterase 2A (PDE2A)	Phosphodiesterase	-	-	0.101613854776	-
Phosphodiesterase 10A (PDE10A)	Phosphodiesterase	-	-	0.101613854776	-



A: Oral Toxicity Prediction of Orlistat

B: Distribution Graphs of Orlistat

Figure 4: Toxicity Prediction of A: Oral Orlistat, and B: Distribution Graphs of Orlistat



A: Oral Toxicity Prediction of *Garcinia cambogia*

B: Distribution Graphs of *Garcinia cambogia*

Figure 5: Oral Toxicity Prediction of *Garcinia cambogia*

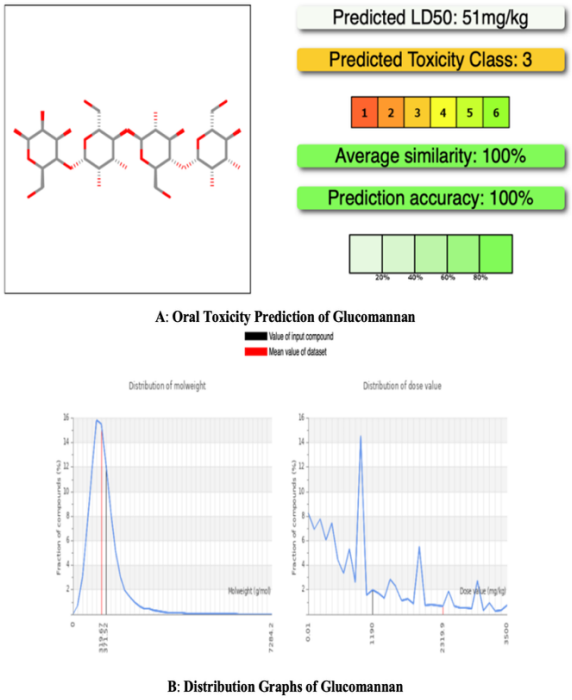


Figure 6: Toxicity Prediction of Glucomannan A: Protox-III Oral Toxicity Prediction of Glucomannan, and B: Distribution Graphs of Glucomannan

Table 11: Predicted Organ Toxicities

Target	Orlistat	Semaglutide	*Garcinia cambogia*	Glucomannan
Hepatotoxicity	0.7	NA	0.64	0.91
Neurotoxicity	0.68	NA	0.68	0.93
Nephrotoxicity	0.86	NA	0.72	0.78
Respiratory toxicity	0.75	NA	0.59	0.95

Active toxicity Active toxicity Inactive toxicity

Table 12: *In Silico* Activity Prediction

Activity	Orlistat		Semaglutide		*Garcinia cambogia*		Glucomannan	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
Pro-opiomelanocortin converting enzyme inhibitor	0.919	0.004						
Saccharopepsin inhibitor	0.893	0.005						
Acrocylindropepsin inhibitor	0.893	0.005						
Chymosin inhibitor	0.893	0.005						
			-	-				
			-	-				
			-	-				
			-	-				
ATP citrate lyase inhibitor					0.971	0.000		
Lipid metabolism regulator					0.871	0.004		
Antidiabetic activity					0.708	0.006		
Hypolipemic activity					0.543	0.031		
Antidiabetic							0.777	0.005
Alpha glucosidase inhibitor							0.844	0.001
Lipotropic							0.875	0001
Lipid metabolism regulator							0.435	0.076

In Silico Methods

The results show that the compounds differ primarily in their properties because of differences in molecular size and structure.

Pharmacokinetics

Table 9 is a summary of the key pharmacokinetic and physicochemical characteristics of Orlistat, Semaglutide, *Garcinia cambogia*, and Glucomannan. Orlistat is highly lipophilic and has low gastrointestinal absorption, so it has a local effect in the gastrointestinal tract rather than a widespread effect in the bloodstream. The mechanism of action is blocking lipase enzymes in the digestive system, thereby limiting the digestion and absorption of dietary fats and helping to reduce calorie consumption. On the other hand, the computational predictions provided no reported values for most of the pharmacokinetic parameters of Semaglutide. This is probably because Semaglutide is a large, complex peptide with a high molecular weight, whereas the prediction tools used are typically designed for small chemical

compounds. As a result, the system may not be able to accurately predict its pharmacokinetic properties. However, Semaglutide is a well-established medication with a long clinical history as a glucagon-like peptide-1 (GLP-1) receptor agonist used to control appetite, promote insulin release, and support weight loss. Likewise, *Garcinia cambogia* has moderate solubility and is predicted to be more soluble in the gastrointestinal tract. These characteristics suggest that it can be better absorbed after oral intake and may affect the metabolic functions associated with weight loss and energy balance. Conversely, glucomannan has a higher molecular weight and more hydrogen-bond acceptors and donors, which also contributes to its high-water solubility. Nevertheless, its gastrointestinal absorption and bioavailability are low, despite its high solubility. This means glucomannan is not readily absorbed into the bloodstream and works mainly in the gastrointestinal tract. Here, it absorbs water and forms a gel-like material that retards digestion, enhances satiety, and helps reduce food intake, aiding weight control. (Table 9, Figure 3)

Pharmacodynamics

Table 10 shows the predicted pharmacodynamic targets of Orlistat, Semaglutide, *Garcinia cambogia*, and Glucomannan, explaining how these compounds may interact with different proteins in the body.

As indicated in the table, Orlistat has predicted interactions with enzymes involved in lipid metabolism, including monoacylglycerol lipases and other lipid-related enzymes. These enzymes have been seen to play an important role in the metabolism of dietary fats during the digestion of food in the body. Orlistat's interaction with these enzymes prevents the normal metabolism of triglycerides into fatty acids, which the body absorbs during digestion. Consequently, some of the dietary fat consumed by the body is not absorbed by the intestine and is excreted from the body, explaining the known pharmacological action of Orlistat as a lipase inhibitor. By inhibiting fat absorption in the digestive system, Orlistat reduces the overall calories consumed, resulting in weight loss in obese individuals.

Next, we observed that semaglutide did not show the predicted pharmacodynamic targets. This may be attributed to the fact that the prediction tools may not be able to analyse large peptide molecules. However, semaglutide is a well-established glucagon-like peptide-1 (GLP-1) receptor agonist that enhances insulin secretion, decreases appetite, and slows gastric emptying.

Next, *Garcinia cambogia* showed predicted interactions with various proteins. The proteins predicted were histone deacetylases (HDAC1 and HDAC6), the androgen receptor, and transport proteins such as P-glycoprotein (ABCB1) and sulfonylurea receptor 2 (ABCC9). Histone deacetylases regulate various cellular functions and are responsible for the regulation of various genes. The androgen receptor regulates hormone signalling. Transport proteins such as P-glycoprotein regulate the transport of substances through the cell membrane. The interaction of *Garcinia cambogia* with these proteins may suggest its involvement in regulating metabolic pathways related to energy balance, which may influence body weight.

Lastly, Glucomannan has relatively weak predicted interactions with various proteins such as vascular endothelial growth factor A (VEGFA), fibroblast growth factors, heparanase, cyclin-dependent kinase 1, and galectins. These proteins are involved in cell communication, growth, and regulation rather than fat digestion or metabolism. The weak interaction with Glucomannan is further supported by the relatively low interaction values obtained for these proteins. This implies that Glucomannan does not have a strong affinity for any particular molecular target. This observation is also consistent with the known mechanism of action for Glucomannan, which is a soluble dietary fiber rather than a drug that specifically interacts with particular receptors. Instead, glucomannan works in the digestive system by trapping water to form a gel-like substance that promotes fullness and reduces food intake. (Table 10)

Safety and Toxicity of Drugs

To begin, we assessed the potential toxicity of orlistat using the ProTox-III prediction model. The analysis indicated that the compound has a predicted LD_{50} of 1300 mg/kg, placing it in the IV^{th} toxicity class. The LD50 value is widely used to express the amount of the compound that may cause adverse effects in 50% of the experimental model, and it aids the researcher in determining the acute toxicity of the compound Therefore, the compound has the potential to cause harm if ingested, although relatively higher doses of the compound are required to induce significant toxic effects on the body, as compared to the compound in the lower toxicity classes This model also showed an average similarity of 62.99% and a prediction accuracy of 68.07%, which means that this prediction was generated based on the chemical structure of Orlistat compared with similar compounds in this model's database. Additionally, the distribution graphs in this figure 4 compare Orlistat's molecular weight and predicted dose with those of other compounds in the model's dataset. Orlistat's values fall within the normal range compared with the dataset used by this model, indicating that the model analysed this compound properly and generated a reliable toxicity prediction. (Figure 4)

The computational model did not predict toxicity for semaglutide. However, clinical trials and *in vivo* research provide considerable evidence on semaglutide safety and toxicity. Clinical trials have shown that the most common side effects of taking this drug include gastrointestinal side effects such as nausea, vomiting, and diarrhea. However, severe toxicity of this drug is rarely seen when used at therapeutic doses [18-20]. Thus, although the computational model did not predict toxicity for this drug, there is considerable evidence of its safety. For *Garcinia cambogia*, we evaluated potential toxicity using the ProTox-III prediction model. The results showed that the predicted LD50 value was 1000 mg/kg, which corresponds to a toxicity level of IV. The LD50 is defined as the amount of a substance that may cause adverse effects in 50% of the test models, and this is commonly used as an estimate of acute toxicity. Compounds in this category are considered harmful if ingested, but they require a higher dose to cause toxic effects than compounds in lower toxicity classes. The average similarity was 58.88%, and the accuracy was 67.38%, indicating that the prediction was based on the similarity between the chemical structure of *Garcinia cambogia* and compounds in the model's database. The distribution graph for the molecular weight and predicted dosage of the compound, shown in the figure, compares these values with the dataset used by the model. As with Orlistat, the values for *Garcinia cambogia* fall within the normal range. (Figure 5)

Lastly, for Glucomannan, the ProTox-III model predicted an LD_{50} value of 51 mg/kg, which classified the compound in toxicity class III. In addition, the model indicated 100% similarity and 100% prediction accuracy, indicating high confidence in the prediction because similar compounds were present in the prediction database. The organ toxicity results indicated a low predicted risk for hepatotoxicity (0.91), neurotoxicity (0.93), and respiratory toxicity (0.95). However, a possible risk of nephrotoxicity (0.78) was also indicated, which suggests that the kidneys are more sensitive to possible toxic effects. Moreover, the distribution graphs in the figure above suggest that the molecular weight and dose of the compound (i.e., glucomannan)

fall within the range used in the dataset for prediction, supporting the prediction results. (Figure 6)

In conclusion, Protox-III toxicity predictions indicate that glucomannan generally has a better safety profile than orlistat, semaglutide, and *Garcinia cambogia*. The results suggest that glucomannan is unlikely to cause liver or nervous system toxicity, as these were predicted to be inactive. However, possible kidney and respiratory toxicity were predicted, which means these effects should be investigated further. Overall, glucomannan appears to be safer in some aspects, particularly for the liver and nervous system, but additional experimental and clinical studies are needed to confirm its overall safety. (Table 11)

Prediction of Activity

The selected activity parameters show high predicted biological activity (Pa > Pi and Pa > 0.7). (Table 12)

Table 12 indicates that these mechanisms may play a role in processes related to weight management. Pro-opiomelanocortin converting enzyme inhibitor activity is associated with the pro-opiomelanocortin (POMC) pathway, which regulates appetite, satiety, and overall energy balance. Modulation of this pathway can influence food intake and may contribute to weight control. In addition, saccharopepsin inhibitor, acrocylindropepsin inhibitor, and chymosin inhibitor are predicted to inhibit proteolytic enzymes involved in digestive processes. Inhibition of these digestive enzymes may affect nutrient breakdown within the gastrointestinal tract, which may indirectly influence energy uptake from consumed nutrients.

These predicted activity profiles are consistent with the mode of action of Orlistat, an anti-obesity drug used to manage obesity and promote weight loss by inhibiting gastric and pancreatic lipases in the gastrointestinal tract. By inhibiting lipase activity, Orlistat reduces the absorption of a significant portion of dietary fats, thereby reducing the diet's caloric content and promoting weight loss. The predicted activity profiles for enzyme inhibition observed in the analysis further underscore the importance of modulating digestive enzymes for managing obesity and weight loss.

The biological activities expected from *Garcinia cambogia* also suggest its potential for weight management and metabolic control. Its high likelihood of inhibiting ATP citrate lyase could decrease fatty acid and cholesterol synthesis, which in turn could help reduce the amount of fat accumulated in the body. Moreover, its predicted biological activity in regulating lipid metabolism and acting as a hypolipemic agent could help control fat accumulation in the body and reduce blood lipid levels. In addition, the predicted antidiabetic activity suggests that Garcinia could improve glucose metabolism in the body.

In contrast, no activity was predicted for semaglutide using the PASS prediction model. This does not imply that semaglutide is devoid of biological activity. The most likely reason is that semaglutide is a large, high-molecular-weight peptide, and the PASS system is primarily designed to predict small chemical compounds. Therefore, this model may not be able to detect or predict semaglutide's activity. However, it is well known for its clinical activity in treating obesity and type 2 diabetes, as it reduces appetite, slows gastric emptying, and increases insulin secretion.

Lastly, the results showed that glucomannan has several predicted activities, which include antidiabetic activity, alpha-glucosidase inhibition, lipotropic activity, and regulation of lipid metabolism. These activities are important because obesity is closely linked to problems affecting glucose and fat metabolism. For instance, the antidiabetic activity of glucomannan suggests it could help improve blood sugar levels. This is very important, given that some obese individuals also experience diabetes. Alpha-glucosidase inhibition suggests that glucomannan could slow carbohydrate metabolism, meaning glucose is absorbed into the bloodstream more slowly after a meal. This is important because slower glucose absorption can prevent sudden increases in blood sugar, which may help an obese person feel full longer and reduce the amount of food they consume. The second predicted activity is lipotropic, which relates to fat metabolism. Compounds with lipotropic properties may also assist the body in utilising the reserve of fat as energy, rather than allowing the buildup of fat in the tissues of the body. Finally, by regulating lipid metabolism, the compound may affect how the body metabolises, transports, and stores fat, which may also help reduce fat buildup and maintain healthy metabolism. These are the possible actions of the compound; as such, it may help manage obesity through mechanisms such as regulating glucose, carbohydrate digestion, fat metabolism, and lipid metabolism.

RESULTS AND DISCUSSIONS

The results from clinical studies and *in silico* analysis provide insights into the safety and efficacy of orlistat and *Garcinia cambogia* for weight loss.

Orlistat: Efficacy and Safety

The clinical studies reported in Tables 1 and 2 clearly indicate that orlistat is effective for weight loss in obese individuals. In a multicenter randomised trial by Acharya *et al*. (2006), body weight decreased from 97 kg to 88.8 kg in orlistat-treated subjects, compared with 91.8 kg in placebo-treated subjects after 12 months of treatment. Similarly, Jain *et al*. (2011) showed that body weight decreased from 80.2 kg to 75.55 kg in subjects receiving orlistat, whereas placebo-treated subjects decreased from 79.8 kg to 77.3 kg. In addition, improvement was also observed in other metabolic factors, such as a reduction in BMI from 29.6 kg/m² to 27.7 kg/m² and a reduction in waist circumference from 102.3 cm to 97.5 cm. Another clinical study by Guy-Grand *et al.* (2004) showed that orlistat reduced LDL cholesterol from 145 mg/dL to 128 mg/dL, which benefits cardiovascular health. Regarding safety, Table 1 indicates that the most commonly reported adverse effects were gastrointestinal, such as steatorrhea, oily stools, and diarrhoea, which result from orlistat's mechanism of action, which involves blocking fat absorption. However, the adverse effects were generally mild, and severe adverse effects were infrequent, suggesting that orlistat is generally well tolerated.

For *Garcinia cambogia*, the clinical trials in Tables 5 and 6 show mixed outcomes for weight loss. In the randomised study by Hayamizu *et al.* (2003) [21], *Garcinia cambogia* supplementation led to a reduction in visceral fat area from 131 cm² to 114 cm², or approximately a 13% reduction, although the change in body weight was small. In another clinical trial by Acharya *et al.* (2006)[15] and Maia-Landim *et al*. (2018)[22], *Garcinia cambogia* supplementation combined with glucomannan reduced body weight from approximately 92.4 kg to 85.3 kg, along with reductions in fat mass and cholesterol levels. However, the randomised controlled trial study by Heymsfield *et al*. (1998)[23] found that the reduction in body weight with *Garcinia cambogia* supplementation (from 92.1 kg to 88.9 kg) was not significantly different from the placebo (from 92.3 kg to 88.2 kg). This suggests that *Garcinia cambogia*'s efficacy in reducing weight may vary across studies. Regarding safety, the studies indicated that *Garcinia cambogia* was well tolerated, with no serious adverse effects observed in the trials. Overall, the results suggest

that although *Garcinia cambogia* may offer certain metabolic benefits, its efficacy in reducing weight may be less consistent than other pharmacological interventions, such as orlistat.

Semaglutide Efficacy and Safety

The *in silico* and *in vivo* clinical trial data provide crucial information on the safety and efficacy of semaglutide and glucomannan for weight loss management. From the semaglutide clinical trials included in the tables, the evidence for the drug's efficacy in weight loss is strong. In the STEP-1 trial by Wilding *et al*. (2021), for example, 86.4% of participants receiving the drug had at least 5% weight loss, compared with 31.5% receiving placebo. In addition, 69.1% had at least 10% weight loss, compared with 12.0% among those receiving placebo. In this study, 50.5% had ≥15% weight loss compared to only 4.9% receiving the placebo. In addition to weight loss, the drug also showed efficacy for other clinical outcomes, such as reducing waist circumference by −13.5 cm compared with −4.1 cm for placebo. The drug also reduced systolic blood pressure by −6.2 mmHg compared with −1.1 mmHg for placebo. The safety information in Table 3 shows that the drug's side effects were mostly gastrointestinal. For instance, nausea occurred in 44% of patients, compared with 17% in the placebo group, while vomiting occurred in 25% of the semaglutide group, compared with 7% in the placebo group. In addition, diarrhoea occurred in 32% of the semaglutide group, compared with 16% in the placebo group. Despite these adverse effects, the rate of drug discontinuation due to adverse effects remained low (7.0% vs 3.1% in the placebo group), suggesting the drug was well tolerated.

For glucomannan, the *in silico* analysis predicted several biological activities that may be useful for weight management. These activities include anti-diabetic activity, alpha-glucosidase inhibition activity, lipotropic activity, and lipid metabolism regulation. The predicted activities of glucomannan suggest potential utility in improving glucose metabolism, slowing carbohydrate digestion, and regulating fat metabolism. The toxicity prediction of glucomannan estimated an LD_{50} of 51 mg/kg, and therefore glucomannan was assigned to toxicity class III. The organ toxicity prediction for glucomannan showed low predicted risk of hepatotoxicity and neurotoxicity. However, it also indicated a potential risk of nephrotoxicity. As shown in tables of *in vivo* clinical studies of various compounds, glucomannan had a good safety profile. In Walsh *et al.* (1984), subjects who took 3 g/d of glucomannan for 8 weeks showed significant weight loss of −5.5 lbs compared with placebo. This study also found that glucomannan supplementation significantly reduced total cholesterol by −21.7 mg/dL and LDL cholesterol by −15.0 mg/dL. In another study by Keithley *et al.* (2013), where participants received 3.99 g/day for 8 weeks, weight change was small for those who took the supplement (-0.40 kg) compared with those who took a placebo (-0.43 kg). This indicates that the effect of the supplement may vary. Regarding safety, most adverse events were mild gastrointestinal symptoms such as bloating, fullness, and burping. However, the clinical trials reported no severe adverse events or deaths. Moreover, laboratory results, such as liver enzymes and creatinine, were normal.

CONCLUSION

In conclusion, among the compounds studied, semaglutide appears to be the best choice for weight management, as it has been shown to cause significant weight loss. Orlistat is also an effective choice, but it is often accompanied by gastrointestinal side effects. In contrast, natural compounds like *Garcinia cambogia* and glucomannan have weaker weight-loss effects but are safe.

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