JOURNAL OF CLINICAL IMMUNOLOGY AND MICROBIOLOGY

E-ISSN: 3068-5168
Journal of Clinical Immunology & Microbiology

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

Modulation in Gut-Brain Axis via Food Supplements and its Effect in Obese Animal Models: A Systematic Review

Jitendra Kumar Patel[1], RS More[1*], Amit Kumar Nayak[1], Alakh Narayan Singh[2]

[1]Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

[2]Department of Microbiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

***Correspondence author:** RS More, Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India;
Email: psychiatry.more@gmail.com

Citation: Patel JK, et al. Modulation in Gut-Brain Axis via Food Supplements and its Effect in Obese Animal Models: A Systematic Review. J Clin Immunol Microbiol. 2025;6(3):1-11.

https://doi.org/10.46889/JCIM.2025.6303

Received Date: 12-08-2025

Accepted Date: 29-09-2025

Published Date: 06-10-2025

Abstract

Obesity is a globally emerging social burden with a cost of huge percentage loss of the world's Gross Domestic Product (GDP). This review attempts to explore whether or not modulation in the gut-brain axis with various drugs or supplements is an effective strategy to overcome obesity.

A systematic literature review was performed searching database sources PubMed, Cochrane Library, Web of Science and Scopus using keyword combination "Gut-Brain Axis and Obesity" following PRISMA guidelines. The summaries of included studies were compiled in a comparative table to show the effective roles of different drugs and supplements in prevention of obesity.

Obesity results in due to disproportion in nutritional intake and physical output. Proper regulation needs one to check their daily diet intake. According to studies, feeding behaviour impacts gut microbiota establishment, which synthesises metabolites that lead to an impact on body physiology via the Gut-Brain Axis. This study concluded that during obesity, the diversity of microbes and Bacteroidetes to Firmicutes ratio decrease significantly. Firmicutes includes LPS-producing Gram-negative bacteria, which cause inflammation by disrupting the integrity of blood-brain barrier and gut barrier. These microbes also promote upregulation of proinflammatory genes like IL-6, TNF-α and downregulation of ZO-1, occludins, which encode tight junction proteins. Imposing Ayurvedic supplementation or pharmaceutical drugs reverses these changes by restoring Bacteroidetes, which is marked by beneficial bacterial genera that magnify production of SCFAs. Entering in bloodstream, SCFA alter the expression of hepatic genes including CYP7A1, HMGCoAS and SCD1- key regulators of lipid metabolism and will also affect leptin receptor expression in the brain, as well as leptin B and adiponectin in the intestine. An alteration in the gut-brain axis employing different supplementation or drugs portrays a promising anti-obesity treatment for reducing obesity or preventing its onset, if considered early.

Keywords: Gut-Brain-Axis; Obesity; α-Diversity; Metabolites; Lipopolysaccharides; Short Chain Fatty Acids; Firmicutes to Bacteroidetes ratio (F/B ratio); Hyperglycemia; Insulin Resistance

Abbreviations:

ND: Normal Diet; CD: Control Diet; NC: NoChange HFD: High Fat Diet; LFD: Low Fat Diet; STZ: Streptozotocin; AA=Arachidonic Acid; LP.S58=Lactobacillus PlantarumS58; B-G: B-Glucan; TBPH: Bis(2-Ethylhexyl)-2;3;4;5-Tetrabromophthalate;CST: Chowiseungcheng-Tang; ORL: Orlistat; XOS: Xylooligosaccharides; HFSD : High-Fat And High-Sugar Diet; DM: DendrobiumMixture; INU=Inulin; MB: Monobutyrin; YBCH: Yak Bone Collagen Hydrolysates; Esps : Excretory Secretory Products; MSG: Monosodiun Glutamate; GP: Guava Polysaccharide; QWS: Quinoa With Saponin; QNS: Quinoa Without SaponinVD: Vitamin D; TMAO=Trimethylamine N-Oxide; TMA=Trimethylamine; LPS: Lipopolysachharide; ESPs:

Excretory Secretory Products; SCFA: Short Chain Fatty Acid; LDL: Low Density Lipid; HDL: High Density Lipid; TG: Triglycerides; TC: Total Cholesterol

Introduction

Obesity is a prominent bulging issue of the era affecting 11% of men and 15% of women (Overall 13%) of the total adults worldwide and the economic impact is anticipated to represent 3.3% of global GDP by 2060 [1-3]. It is forecasted to reach 13.3% in men and 16.9% among women upto 2040 in India [4]. It is defined as "an accumulation of excess body fat that may alter body functions", which is clinically evaluated through the Body Mass Index (BMI), calculated as body weight in kilograms divided by height in meters squared (kg/m^2) [5]. Studies suggest that of people suffering from obesity, 60 – 90% are diagnosed with type 2 diabetes [6-8]. People with increased levels of visceral adipose tissue demonstrate insulin resistance, elevated insulin levels (hyperinsulinemia), impaired glucose tolerance and dyslipidemia marked by increased concentrations of triglycerides and apolipoprotein B, along with elevated LDL and low HDL, inflammation and increased blood glucose levels [9]. Excessive energy intake through nutritional intake and low expenditure is the primary contributor to obesity. Although obesity arises from a complex interplay of genetic, physiological, environmental, psychological, social, economic factors, energy surplus are the key contributor [10]. Metabolic diseases like cardiac disorder, non-alcoholic steatohepatitis, prolonged hyperglycemia and obesity are influenced by microbes that reside in the gut which are impacted by the meal plan [11,12]. Gut microbiota includes more than 100 bacterial species and contains a genetic repertoire almost 150 times greater as opposed to the human genome. Although bacteria are predominant residents, the intestine also harbours protozoa, viruses, archaea and fungi. This complex and ever-changing ecosystem shifts across an individual's lifetime, shaped by influences like diet, genetic makeup and age [13]. Taste preferences and medications are major variables of intestinal flora composition. It is a key component to understanding human health, the immune system and metabolic and neurobehavioural traits [14]. The bidirectional communication between the intestinal flora and the central nervous system is referred to as the gut-brain axis [15]. Studies suggest existence of a close interactions between the gut-brain axis and obesity regulation [16]. The Probiotics and Prebiotics food supplements increase beneficial bacteria in the gut. A high-fibre diet mitigates maternal obesity-induced cognitive and social impairments in progeny through alteration of the gut-brain axis. The metabolite-like SCFAs (Short Chain Fatty Acids) are created by saccharolytic genera *Clostridium, Eubacterium, Lactobacillus* and *Ruminococcus* are generated by microbial fermentations of meal fibres and likely impact a broad range of physiological processes in the host [17,18]. The most abundant SCFAs created are acetate, required for the growth of other bacteria. Propionate is relocated to liver and controls gluconeogenesis and hunger sufficiency through coaction with intestinal fatty acid receptors. Butyrate produced by many species of Firmicutes has favourable results on glucose in colonocytes, energy balance and is able to initiate apoptosis in colon cancer cells [19,20]. The fermentation of Protein lead to SCFA production but commonly generates Branched-Chain Fatty Acids (BCFAs) specifically isobutyrate, 2-methylbutyrate and isovalerate in the distal colon that have been proposed as potentially harmful to metabolic health and gut integrity, treatment with mixtures of dietary fibres causean increase in carbohydrate fermentation and inhibit protein fermentation supposed to reduce obesity [21,22]. The meal high in fat causes boost in intestinal Lipopolysaccharides (LPS) by producing bacterial species, resulting in inflammation, reduction of tight junction proteins thus and elevations in circulating LPS, resulting in metabolic endotoxemia and insulin resistance [23,24]. These metabolites may impact on gut or raise in serum or organs and enable linking with brain and make sense of what has been eaten [25,26]. The prominent microbial phyla identified in the gut include the bacterial group Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, Verrucomicrobia, Fusobacteria and Cyanobacteria-like organisms, along with the archaeal phylum Euryarchaeota [27]. The presence of Bacteroidetes to Firmicutes (B/F) ratio in the intestine is a determinant factor for obesity and a decrease in the B/F ratio is positively correlated with high-fat diet-induced obesity in mice [28-30]. Therefore, in this study, we try to find out whether the modulation in the gut-brain axis through different drugs or any kind of supplement is an effective strategy to overcome obesity or not.

Materials and Methods

The systematic review writing was done by following the norms of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [31].

Search Strategy and Screening

The thorough literature surveys includes PubMed, Cochrane Library, Web of Science and Scopus database by using the search term "Gut-Brain Axis AND Obesity". For further filtration, only "Research Article" option was selected in the automation tools of the search database. Duplicates were removed manually by copying all the titles to the word file from all databases and finding

a match for the title in another database file. After the removal of duplicates, the screening of records is done based on titles and abstracts. The articles that were unable to be accessed or unable to check the inclusion criteria were excluded. Sorted full-text articles were downloaded in PDF format and thoroughly examined. Publications that have shown the interactions between obesity induced in animal models and modulation in intestinal flora profiles due to the treatment with drugs or supplements are compared to establish the coactions in Gut-brain Axis in obesity.

Inclusion and Exclusion: The study selection was performed independently by three authors (J. K. Patel, A.K. Nayak and R.S. More). Any dissonance between the two investigators was discussed until an agreement was reached. Full-text articles were selected according to the following exclusion and inclusion criteria:

Exclusion Criteria

(1) Descriptive reviews, systematic reviews and meta-analysis; (2) Books or book chapters; (3) Editorials, letters to the editor, thesis and shorts reports; (4) Studies included human samples; (5) *In-vivo* studies; (6) Clinical trials; (7) Articles published in another language except English.

Inclusion Criteria

(1) Animal model study; (2) Induced obesity; (3) Original articles having obesity and Gut microbiota interactions; (4) Supplementation or drug treatment.

Fetching Data

The data pulled-out from published paper contains variables like authors/ publication year, Strain, Model organism, Sex, age/weight, study duration, obesity induction, duration, supplement or drug dose/ administration route and microbiota findings α Diversity, Phylum increase or decrease, F/B ratio, Genus increase or decrease and metabolites produced).

Results

Search Summary

Total (n=9587), (PubMed n =511, Web of Science n =680, Scopus n=8364, Cochrane Library n=32) search results were obtained from the above-mentioned databases. By applying automation tools (n=6566), articles were filtered out, after removing duplicates (n =213) and remaining records (n=2808) were screened by titles /abstract and removed by applying inclusion and exclusion criteria (n=2575). Full-text articles (n=233) downloaded, examined and discarded (n=178) that do not fit in inclusion criteria. Finally, (n=55) studies were considered for the review, since (n=27) studies did not include Gut microbiota sequencing data, ultimately (n=28) were incorporated in systematic review (Fig. 1).

Observational Studies

Summary of the study is presented in Table 1. All studies incorporated in the review were published between 2016-2024 and were done on various animal models. The results suggested an association between obesity and alterations in gut microbiota due to food intake patterns. Out of 29 studies, 7 were done on male rats, 21 on mice (18 males, 02 females, 01 male + female) and 01 study on fish. Mainly, obesity is induced by HFD (45% or 60% calories from fat) alone or along with STZ. Two studies suggest that Monosodium Glutamate (MSG) and Bis (2-ethylhexyl)-2,3,4,5-Tetrabromophthalate (TBPH) are also utilized to induce obesity in animal models. 94.4% diet induced obese models show decreased α Diversity (species richness) indexed by Shannon's and Simpson indices, ACE or Chao 1 index and 17 out of 28 diet-induced model organisms have decreased Bacteroidetes/Firmicutes ratio (B/F ratio), which is an indicator of obesity. Both α Diversity and B/F ratio get back equivalent levels to control after treatment with different drugs or supplements. Results showed a significant level up in bacterial phylum Firmicutes, Actinobacteria and Proteobacteria whereas the level down in Bacteroidetes and Cyanobacteria in obese mice as compared to the normal mice. This is reversed to normal due to different treatments. The alteration in gut microbiota causes changes in metabolites produced in the body. Three studies showed an increase in LPS levels during obesity, 10 studies suggest an alteration in SCFAs levels and 1 shows a change in TMAO and TMA levels.

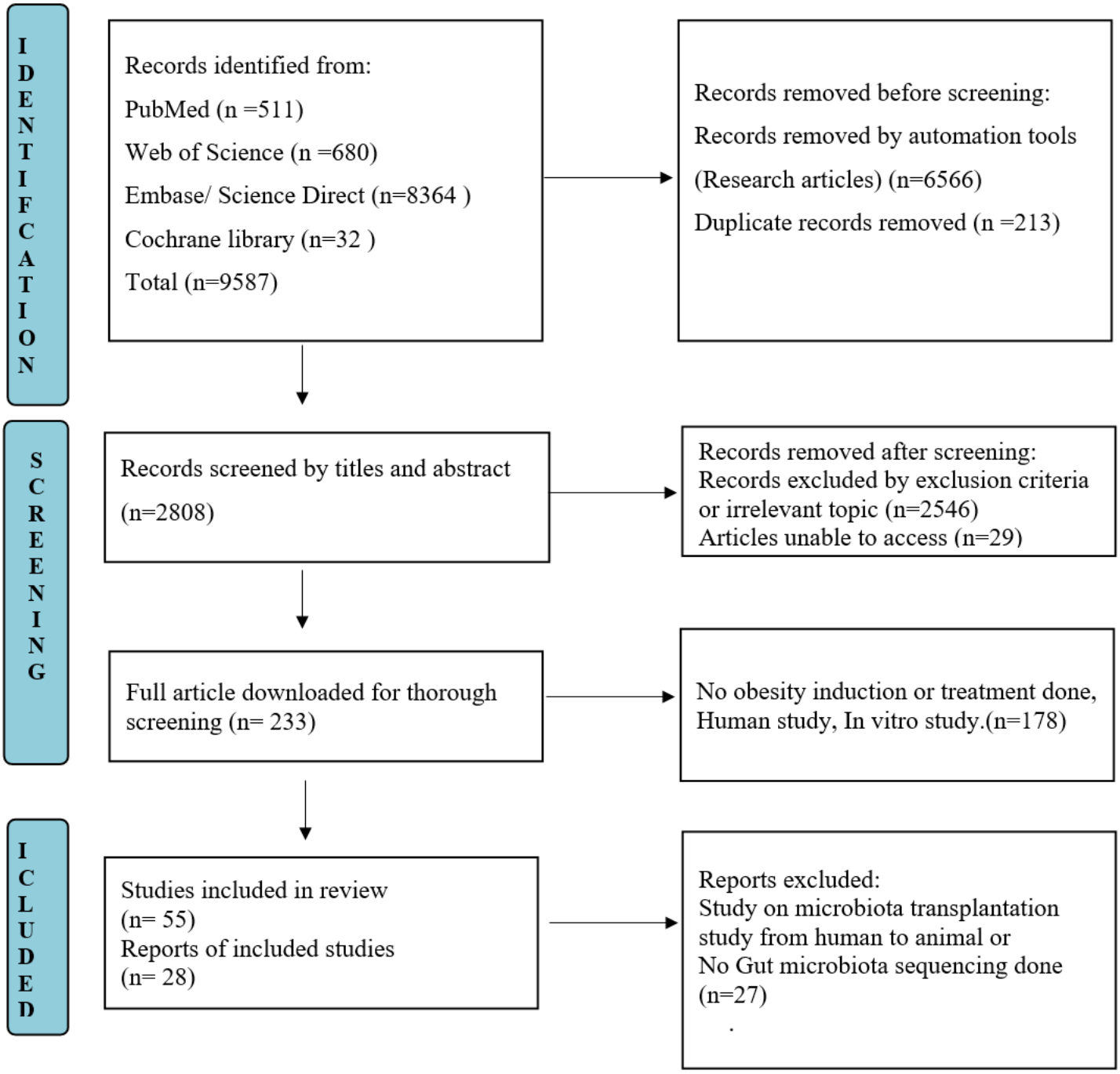

Figure 1: Shows the flow chart for the database search and screening.

S N	Author and Year	Strain/Model organism/ Sex	Age/ Weight	Study Duration	Obesity Induction	Supplement/ Drug (Dose)	Administration route	Microbiota findings				
								α Diversity	B/F ratio	Phylum	Genus	Metabolites
1	Klingbeil, et al., 2024 [32]	Wistar Rats, Male	----------	7 weeks	HFD	Paired fed High fat diet	Orally	↑	↑	Bacteroidetes↑, Firmicutes↓, Verrucomicrobia ↑	*Lactococcus* ↓, *Streptococcus* ↓, *Coproccoc*↓ *Enterobacteriaceae* ↓, *Burkholderiales* ↓, *Bilophila* ↓, *Muscispirillum* ↓	----------
2	Zheng, et al., 2022 [33]	Sprague-Dawley Rats, Male	6 weeks, (200 ± 20 g)	10 weeks	HFD + STZ	DM (10.8 g/kg) and Metformin (100 mg/kg)	Intragastric	↑	↑	Bacteroidetes↑, Firmicutes↓, Actinobacteria ↓	*Lactobacillus*↑, *Blautia*↑, *Oscillospira*↑, *Ruminococcus*↓, *Allobaculum*↓	LPS↓
3	Hussein, et al., 2021 [34]	Wistar rats, Male	8 weeks, 150–200 g	8 weeks	HFHS + STZ	Metformin (200 mg/kg) VD (500 IU/kg)	Orally	-----	↑	Bacteroidetes↑, Firmicutes↓	---------	---------
4	Wang, et al., 2019 [35]	Sprague-Dawley Rats, Male	5-6 weeks (220 ± 20 g)	12-week	HFD	Acupuncture	0.30×25mm needles	NC	↑	Bacteroidetes↑, Cyanobacteria ↑, Firmicutes↓, Proteobacteria ↓	*Prevotella* ↑	--------
5	Chunchai, et al., 2018 [36]	Wistar Rats, Male	180-200g	24 weeks	HFD + STZ	Prebiotic (XOS, 10%, 1ml/day), Probiotic (L. paracasei HII01, 10^8cfu 1 ml/day) and Symbiotic (XOS + L. paracasei HII01 and 2 ml/day)	Orally	-------	↑	----------	--------	LPS↓
6	Huang, et al., 2018 [37]	Sprague-Dawley Rats, Male	5 weeks	5 weeks	HFD	*Enterococcus faecium*WEFA23 (5.0 × 109 cfu/mL 1ml/day	Orally	↑	-----	Bacteroidetes↑, Proteobacteria ↑, Firmicutes↓,Fusobacteria↓	*Helicobacteraceae*↑, *Veillonelaceae*↑ *Rikenellaceae*↓, *Peptococcaceae*↓, *Odoribacteraceae*↓, *Pseudomonadaceae*↓	TMAO↑, TMA↑
7	Sun, et la., 2016 [38]	Sprague-Dawley rats	12 weeks	96 weeks	HFD	Berberine (150 mg/kg)	Orally	↓	↑	Bacteroidetes↑, Firmicutes↓, Proteobacteria ↑	*Anaerofilum*↑, *Sutterella*↑, *Bilophila*↑, *Desulfovibrio*↑, *Dorea*↓, *Roseburia*↓, *Blautia*↓	SCFA↑
8	Kim, et al., 2022 [39]	C57BL/6J Mice, Male	10 weeks	10 weeks	HFD	*Kimchi (*120 mg/day, 3ooul)	In drinking water or orally	NC	NC	Verrucomicrobia↑	*Akkermansia*↑, *Anaerotruncus*↓	SCFA↑
9	Wang, et al., 2022 [40]	C57BL/6 mice, Male	6 weeks	14 weeks	HFD	Metformin (1g/100g), QWS and QWS (2g/mice)	Orally	NC	↑	Bacteroidetes↑, Actinobacteria ↓, Proteobacteria ↓	*Lactobacillus*↑,*Desulfovibrio*↑,*Adlercreutzia*↑, *Cupriavidus*↓, *Blautia*↓	-------
10	Li, et al., 2022 [41]	C57BL/6 mice	7 weeks	11 weeks	HFD	GP (100 mg/kg)	Orally	NC	↑	Bacteroidetes↑,Actinobacteria↑, Firmicutes↓,	*Clostridium*↑, *Enterorhabdu*↑,*Parvibacter*↑, *Mucispirillum*↓, *Escherichia*↓	Acetic acid↑, Propionic acid↑,

										Proteobacteria ↓		Butyric acid↑
11	Hu, et al., 2022 [42]	C57BL/6 J mice, Male	9 weeks	16 weks	HFD	M-BG, C-BG (500 mg/kg) and O-BG (7% by food weight)	With feed	↓	___	Firmicutes↑, Bacteroidetes↓, Proteobacteria ↓	--------	----------
12	Guo, et al., 2022 [43]	C57BL/6 J mice, Male	6 weeks	12 weeks	HFD	YBCH (0.5, 1.0 and 2.0 g/Kg)	----------	NC	↑	Bacteroidetes↑, Firmicutes↓	*Muribaculaceae*↑, *Alistipes*↑, *Faecalibaculum*↓ *Rikenella*↓	----------
13	Shao, et al., 2021 [44]	16 SPF Kunming mice, Male	4 weeks (20 ± 2 g)	90 days	HFD + STZ	F31 (2000, 180 and60 mg/kg)	Orally	↑	↑	Bacteroidetes↑, Firmicutes↓,Proteobacteria↓, Epsilonbacteraeota↑	*Alloprevotella*↑, *Ruminiclostridium*↑, *Peptococcacea*↑, *Tyzzerella*↑, *Desulfovibrionaceae*↓ *Acetatifactor*↓, *Lactobacillus*↓	SCFA↓
14	Zhou, et al., 2021 [45]	C57BL/6 mice, Male	8 weeks, 20 ±3 g)	12 weeks	HFD	β-elemene (7.5 mg/kg, 0.2 mL)	Orally	-------	↑	Firmicutes↓, Actinobacteria ↑, Verrucomicrobia↑	*Coriobacteriale*↑, *Verrucomicrobiales*↑, *Clostridiales*↓, *Negativicutes*↓	--------
15	Pan, et al., 2021 [46]	C57Bl/6J male mice, Male	9 weeks	7 days and 15 weeks	HFD	β-glucan (500 mg/kg)	With feed	↓	↑	Actinobacteria ↑, Firmicutes↓, Proteobacteria ↓	--------	LPS↓
16	Ma, et al., 2021 [47]	C57BL/6 J Mice, Male	8 weeks	24 weeks	HFD	Metformin (250 mg/kg)	Orally	↑	-----	Bacteroidetes↑, Firmicutes↓, Actinobacteria ↓	----------	------
17	Zhao, et al., 2021 [48]	C57BL/6 J mice, Male	Neonate	18 weeks	MSG (3mg/g)	Quercetin (5mg/kg, 100 µL/10 g)	Subcutaneously	↓	↑	Bacteroidetes↑, Firmicutes↓ B/F ratio-Increased	*Bacteroides*↑, *Akkermansia*↑	SCFA↑
18	Wu, et al., 2021 [49]	C57BL/6 J mice, Male	8 weeks	12 weeks	HFD	ESPs (20 ug twice a week)	Intraperitoneally	↑	↑	Bacteroidetes↓, Proteobacteria ↓, Firmicutes↑	*Dubosiella*↑, *Odoribacter*↑	SCFA↑
19	Yang, et al., 2020 [50]	C57BL/6 J mice, Male	9 weeks	15 weeks	HFD	Curdlan (500 mg/kg)	With feed	NC	↑	Bacteroidetes↑ ,Proteobacteria↑, Firmicutes↓, Actinobacteria ↓	*Alloprevotella*↑, *Alistipes*↑, *Helicobacter*↑, *Ruminiclostridium*↑, *Defluviitaleaceae_UCG_011*↑, *Eubacteriumfissicatena_group*↑, *Ruminococcaceae_UCG_004*↑, *Tyzzerella*↑	LPS↓
20	Biyong, et al., 2020 [51]	C57BL/6 J mice, Male	3 weeks	16 weeks	HFSD	Retinol (5 IU/g and 25 IU/g)	With feed	↑	-----	----------	*Subdoligranulum*↑, *RC9*↓	NC
21	Lee, et al., 2020 [52]	C57/BL6 Mice, Male	6 weeks	6 week	HFD	2'-fucosyllactose (10% w/v)	In drinking water	--------	------	Bacteroidetes↑	*Peptococcus*↑, *Atopobiaceae*↑, *Oscillibacter*↑, *Marvinbryantia*↑, *Parabacteroides*↑	Glyceric acid↑, Lactic acid↑, Hexanoic acid↑, Pyruvic acid↑, Butyric acid ↓, Indole-3-acetic acid↓, Serotonin↓

22	Tang, et al., 2020 [53]	C57BL/6 J mice	8 weeks	12 weeks	HFD	LP.S58 (1 × 1010 CFU/ kg) and β-G (500 mg/kg)	Orally	↑	↑	----------	*Lactobacillus*↑, *Dubosiella*↑, *Allobaculum*↑ *Akkermansia*↑, *Turicibacter*↑, *Faecalibaculum*↑, *Helicobacter*↓, *Ruminococcaceae*↓, *Bacteroides*↓	LPS↓
23	Liu, et al., 2020 [54]	C57BL/6 J Mice, Female	10 weeks	8−10 weeks	HFD	*INU (*37 g inulin/1000 kcal)	With feed	-------	↑	Bacteroidetes↑ , Firmicutes↓	*Mycoplasmataceae*↑, *Flexispira*↑, *Desulfovibrionaceae*↓	Acetate↑, Propionate↑, Butyrate↑,Isovalerate↑
24	Diling, et al., 2020 [55]	KM Mice, Male	36 weeks, 18–22 g	12 weeks	HFHS	G. lucidum extract (200, 100 and 50 mg/kg)	Intragastric	↑	---- -	----------	*Lactobacillus*↑, *Bifidobacterium*↑, *Roseburia*↑, *Peptostreptococcaceae*↑, *Blautia*↑, *Turicibacter*↑, *Clostridiales*↓, *Lachnospiraceae*↓, *Oscillospira*↓, *Ruminococcaceae*↓, *Dehalobacterium*↓, *Erysipelotrichaceae*↓	---------
25	Ahmadi, et al., 2019 [56]	C57BL/6 J mice	8-10 weeks	8 weeks	HFD	Inulin, Acorn, Sago (5%)	With feed	↓	↓	Bacteroidetes↑ , Firmicutes↓	*Lactobacillus*↑, *Akkermensia*↑, *Mucispirilium*↑, *Enterococcus*↑, *Clostrium*↑, *Dorea*↑, *Ruminococcus*↑, *Oscillospira*↓, *Desulfovibrio*↓, *Bilophila*↓	Lactate↑, Acetate↑, Propionate↑, butyrate↑
26	Kong, et al., 2018 [57]	C57BL/6 J mice, Female	6 weeks	13 weeks	HFD and HCD	Encapsulated Probiotics (*Lactobacillus acidophilus, Bifidobacteriumlongum*, and *Enterococcus faecalis,* 1:1:1, 2.0 x 10^7 CFU)	Intragastrically	NC	NC	----------	*Allobaculum* ↑, *Alloprevotella*↑ *Lactobacillus*↑ , *Clostridium*↑, *Escherichia/Shigella*↓, *Oscillibacter*↓, *Acinetobacter*↓, *Alistipes*↓, *Anaerotruncus*↓, *Bacteroides*↓	---------
27	Zhuang, et al., 2017 [58]	C57BL/6 J Mice, Male and Female	4 weeks	10 weeks	HFD and LFD	AA (10 g/kg)	Orally	↓	↑	Bacteroidetes↑ , Proteobacteria ↓, Verrucomicrobia↓	*Allobaculum*↓, *Oscillibacter*↓, *Bacteroides*↓, *Lactobacillus*↓, *Bifidobacterium*↓	Acetate↑, Butyrate↓
28	Ansari, et al., 2016 [59]	C57BL/6 J mice	6 weeks	16 weeks	HFD	CST (700 mg/kg) and ORL 10 mg/kg)	Orally	-----	↑	Bacteroidetes↑ , Firmicutes↓	*Akkermansia*↑, *Bifidobacterium*↑, *Rosenburia*↑, *Ruminococcus*↑	----------
29	Zhou, et al., 2021 [60]	Zebra fish, Female	4 months	6 weeks	HFD 24% crude fat	TBPH (0.02 and 2 μM)	Exposed	NC	↓	Bacteroidetes↑ , Firmicutes↑, Proteobacteria ↓, Fusobacteria↓, Actinobacteria ↑	----------	----------

Table 1: Shows the comprehensive effects of different supplements or drugs on gut microbiota profile (α Diversity, B/F ratio, Bacterial Phylum, Genus and Metabolite produced) after treatment in obese animal models.

Discussion

This systematic review showed the role of intestinal microflora composition in developing obesity via gut-brain axis and provided brief insights of different drugs or supplements on animal models. In present study, we tried to portray the possible

underlying mechanisms through which high-fat diet induces obesity and its amelioration by tempering gut microbiota, providing a fibrous diet, prebiotics or probiotics.

Interplay of Gut-Brain Axis in Obesity

Role of Gut microbiota in development of obesity: The studies done by authors show that the animals induced with obesity showed a decrease in gut microbes species richness and increase F/B ratio [32-34,37,39,44,47,49,51,53,55]. Genera belonging to phylum Bacteroidetes like *Lactobacillus, Ruminococcus, Allobaculum* and *Odoribacter* produce metabolites SCFAs including isobutyric acid, isovaleric acid and ethyl methyl acetic acid and Firmicutes are the foremost phyla in gut that are associated with energy biotransformation homeostasis [34,38,39,49,54,56]. Studies show Muribaculaceae break down nutritional polysaccharides to build SCFAs, along with succinate, acetate and propionate [36,46,50]. During obesity proportion of Proteobacteria, which mostly contains gram-negative bacteria belonging to the order *Lactobacillales, Erysipelotrichales* and *Mycoplasma* that produce LPS (36) and Actinobacteria decreased significantly and *Lactobacillus, Bifidobacterium, Oscillospira* and *Blautia* were down-regulated and negatively associated to LPS, fasting blood glucose level, TNF-α and IL-6 [33,46]. The abundance of bacteria genera like *Butyricicoccus, Prevotella, Turicibacter, Saccharibacteria, Ruminococcus, Bifidobacterium, Vampirovibrio, Lachnospiracea, Rikenella, Parasutterella, Roseburia, Parvibacter* and *Clostridium* was negatively associated with body weight gain, serum TG, LDL-C levels, hepatic TG and whereas a positive association was obtained from genera *Oscillibacter, Butyricimonas* and *Acetatifactor* [41]. The dysbiosis in gut microbiota causes inflammation compromised epithelial barrier integrity, causing translocation of LPS along with another bacteria from gut to the body fluid circulation and low expression of ZO-1 and occludin linked with hyperglycemia [34,58]. In this way, any disturbance caused in intestinal microflora composition may lead to change in energy metabolism, which is regulated by microorganisms in the intestine, which is a promoting factor for obesity.

Role of Metabolites Produced by Gut Microbes in Obesity

The studies show a change in gut microbiota that causes increased LPS production during obesity [33,36,46,52]. The increased LPS level in the blood causes gut inflammation (36), activates macrophages and thus increases the pro-inflammatory cytokines like TNF-α and IL-6 through TLR4-NFκB pathway that may induce obesity [46]. The SCFAs metabolites like butyric acid, ethyl methyl acetic acid, isobutyric acid and isovaleric acid were found to be reduced in obesity [33]. Guava polysaccharides supplementation shows increased SCFAs, especially butyric acid [41]. SCFAs elucidate ameliorative properties against inflammation and balanced regulation of glycolipid synthesis, distribution and degradation. Thus, they act as metabolic mediator to attach with gut microbiota of host physiology [44]. The different taxa of bacteria responsible for the different types of SCFAs production, like glyceric acid, were positively associated to Parabacteroides and Atopobiaceae, Lactic acid with Oscillibacter, Indole-3-acetic acid with Blautia and Lactococcus and with Blautia and Roseburia [52]. The intestinal microbes draw a prime role in the synthesis of cecal TMA, which is oxidised into TMAO in the liver that affecting the biotransformation of cholesterol and bile acid, inhibiting CYP7A1 expression [37]. This suggests that a change in diet pattern can cause alteration in gut microbiota and their secretory metabolites that will reach to brain along with blood circulation and cause a modulation in the signalling pattern to food intake behaviour and lipid homeostasis that will ultimately lead to obesity. So, gut-brain axis modulation via supplements or drugs will be a promising anti-obesogenic cure.

Therapeutic Effects of Different Supplements or Drugs in Induced Obesity

The data from Table 1 suggests that high-fat diet (HFD 45% or 60% calories obtained from fat) is one of the most preferred methods to induce obesity in rats or mice animal models, 24% crude fat is used for fish model, another way is High fat High sugar (HFHS) diet [32,37-43,45-60]. Diet induces obese mice to show increased body weight, plasma insulin level, HOMA index, serum Triglycerides, LDL-C, HDL-C and total cholesterol level, which is due to the over-expression of hepatic genes like CYP7A1, HMGCoAS, SCD1, FAS, SCARB1, LDLR and FMO3, as well as intestinal genes, including FGF15 and FXR [40,36,37,47]. STZ and alloxan are commonly used drugs to induce diabetes and hyperglycemia, but they can also be used with HFD or HFHS to induce obesity along with diabetes-like symptoms in animal models [33-35,44,62,63]. MSG-induced obese mouse model shows down regulation of ZO-1 results in low tight junction protein-1, causing disrupted gut barrier, inflamed colon, broken architecture of glandular epithelium, raised lymphocytes infiltration and goblet cell loss [33,48]. DM and ESPs supplementation restores ZO-1 and occludin expression, normalizes tight junction proteins of intestinal barrier and portray neuroprotective effects [33,49]. Berberine treatment elucidates high expression of GLP-1R mRNA in hypothalamic region of brain, resulting in raised insulin sensitivity contributes to glucose metabolism [38]. The prebiotic, probiotic and synbiotics curdlan improved insulin resistance, LDL, cholesterol, fat mass, circulating serum and brain LPS level and also IL-6 mRNA expression in the colon [36,50].

Modulation in gut microbiota through Kimchi supplementation results in increased SCFAs, lowered neuroinflammation caused by broken blood-brain barrier [39]. Guava polysaccharide supplementation regulates glucose homeostasis and insulin sensitivity by suppressing phosphorylated Insulin Receptor Substrate -1 at Ser318 position while promoting the phosphorylation of Protein Kinase B at Ser 473 [41]. 10% 2'-FL supplementation fixed the cholecystokinin-induced inhibition of dietary intake [52]. Prolonged TBPH manifestation causes notable weight gain, adipocyte hypertrophy and subcutaneous fat aggregation by changes in leptin receptors in the brain and leptin B and Adiponectin in the intestine at transcription levels [60]. Review findings draw an idea that diet-induced obesity will be ameliorated by modulating intestinal microflora via the Gut-brain axis pathways. Supplements or drugs change the gene expression patterns that are involved in maintaining the gut barrier or blood-brain barrier integrity or hepatic genes regulate glucose metabolism [64].

Conclusion

Gut-Brain-Axis is a crucial factor in developing and maintaining obesity and this can be modulated by our daily diet intake. The nutritional component decides the abundance of microbes resides in gut and produce particular metabolites like SCFAs or LPS. Upon reaching to the organs like the liver or brain with circulating blood, cause alterations in gene expression, results in modification of energy balance through glucose metabolism, change in hunger and satiety hormones secretion and contributes to development of obesity. The drugs or herbal supplementation elucidate raise in beneficial bacterial genera in intestine that prime role in reducing the global burden of obesity. This systematic review provides extensive analysis on gut microbiota sequencing outputs from various animal model studies regarding the modulation in intestinal microflora composition during obesity, later on treatment with drugs or supplements.

Conflict of Interest

The authors have declared no conflict of interest.

References

1. WHO, Obesity and overweight: Fact Sheet. 2021. [Last accessed on: September 29, 2025] www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Okunogbe A, Nugent R, Spencer G, Ralston J, Wilding J. Economic impacts of overweight and obesity: Current and future estimates for eight countries. BMJ global health. 2021;6(10):e006351.
3. World Obesity, Newsletter. 2022.
4. Luhar S, Timæus IM, Jones R, Cunningham S, Patel SA, Kinra S, et al. Forecasting the prevalence of overweight and obesity in India to 2040. PloS one. 2020;15(2):e0229438.
5. Piché ME, Tchernof A, Després JP. Obesity phenotypes, diabetes and cardiovascular diseases. Circulation research. 2020;126(11):1477-500.
6. Felber JP, Golay A. Pathways from obesity to diabetes. International journal of obesity. 2002;26(2):S39-45.
7. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic medicine. 1998;15(7):539-53.
8. Piché ME, Tchernof A, Després JP. Obesity phenotypes, diabetes and cardiovascular diseases. Circulation research. 2020;126(11):1477-500.
9. Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proceedings of the National Academy of Sciences. 2009;106(36):15430-5.
10. Wright SM, Aronne LJ. Causes of obesity. Abdominal Radiology. 2012;37(5):730-2.
11. DiBaise JK, Zhang H, Crowell MD, Krajmalnik-Brown R, Decker GA, Rittmann BE. Gut microbiota and its possible relationship with obesity. InMayo clinic proceedings 2008;83(4):460-9.
12. Ravussin Y, Koren O, Spor A, LeDuc C, Gutman R, Stombaugh J, et al. Responses of gut microbiota to diet composition and weight loss in lean and obese mice. Obesity. 2012;20(4):738-47.
13. Asadi A, Shadab Mehr N, Mohamadi MH, Shokri F, Heidary M, Sadeghifard N, et al. Obesity and gut–microbiota–brain axis: A narrative review. Journal of Clinical Laboratory Analysis. 2022;36(5):e24420.
14. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018;361.
15. Shirvani-Rad S, Ejtahed HS, Ettehad Marvasti F, Taghavi M, Sharifi F, Arzaghi SM, et al. The Role of Gut Microbiota-Brain Axis in Pathophysiology of ADHD: A Systematic Review. Journal of Attention Disorders. 2022:10870547211073474.
16. Muscogiuri G, Cantone E, Cassarano S, Tuccinardi D, Barrea L, Savastano S, et al. Gut microbiota: A new path to treat obesity. International Journal of Obesity Supplements. 2019;9(1):10-9.
17. Maukonen J, Saarela M. Human gut microbiota: does diet matter? Proceedings of the Nutrition Society. 2015;74(1):23-36.
18. Liu X, Li X, Xia B, Jin X, Zou Q, Zeng Z, et al. High-fiber diet mitigates maternal obesity-induced cognitive and social dysfunction in the offspring via gut-brain axis. Cell Metabolism. 2021;33(5):923-38.

19. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018;361.
20. Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, et al. Gut microbiota functions: metabolism of nutrients and other food components. European journal of nutrition. 2018;57(1):1-24.
21. Von Martels JZ, Sadaghian Sadabad M, Bourgonje AR, Blokzijl T, Dijkstra G, Faber KN, et al. The role of gut microbiota in health and disease. vitro modeling of host-microbe interactions at the aerobe-anaerobe interphase of the human gut. Anaerobe. 2017;44:3-12.
22. Canfora EE, Meex RC, Venema K, Blaak EE. Gut microbial metabolites in obesity, NAFLD and T2DM. Nature Reviews Endocrinology. 2019;15(5):261-73.
23. Boutagy NE, McMillan RP, Frisard MI, Hulver MW. Metabolic endotoxemia with obesity: Is it real and is it relevant? Biochimie. 2016;124:11-20.
24. Gomes AC, Hoffmann C, Mota JF. The human gut microbiota: Metabolism and perspective in obesity. Gut microbes. 2018;9(4):308-25.
25. Stilling RM, van de Okunogbe A, Nugent R, Spencer G, Ralston J, Wilding J. Economic impacts of overweight and obesity: Current and future estimates for eight countries. BMJ Global Health. 2021;6(10):e006351.
26. Wouw M, Clarke G, Stanton C, Dinan TG, Cryan JF. The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? Neurochemistry Iinternational. 2016;99:110-32.
27. Reinshagen M. Neuropods übermitteln Informationen über Nahrungsmittel im Darm über vagale Neuronen in Millisekunden an das Gehirn. Zeitschrift für Gastroenterologie. 2019;57(03):335.
28. Maukonen J, Saarela M. Human gut microbiota: does diet matter? Proceedings of the Nutrition Society. 2015;74(1):23-36.
29. Murphy EF, Cotter PD, Healy S, Marques TM, O'sullivan O, Fouhy F, et al. Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models. Gut. 2010;59(12):1635-42.
30. Sun J, Liao XP, D'Souza AW, Boolchandani M, Li SH, Cheng K, et al. Environmental remodeling of human gut microbiota and antibiotic resistome in livestock farms. Nature Communications. 2020;11(1):1-1.
31. de Noronha SI, de Moraes LA, Hassell Jr JE, Stamper CE, Arnold MR, Heinze JD, et al. High-fat diet, microbiome-gut-brain axis signaling and anxiety-like behavior in male rats. Biological Research. 2024;57(1):23.
32. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372
33. Klingbeil EA, Schade R, Lee SH, Kirkland R, de La Serre CB. Manipulation of feeding patterns in high fat diet fed rats improves microbiota composition dynamics, inflammation and gut-brain signaling. Physiology and Behavior. 2024;285:114643.
34. Zheng Y, Zhou X, Wang C, Zhang J, Chang D, Zhuang S, et al. Effect of dendrobium mixture in alleviating diabetic cognitive impairment associated with regulating gut microbiota. Biomedicine and Pharmacotherapy. 2022;149:112891.
35. Hussein HM, Elyamany MF, Rashed LA, Sallam NA. Vitamin D mitigates diabetes-associated metabolic and cognitive dysfunction by modulating gut microbiota and colonic cannabinoid receptor 1. European Journal of Pharmaceutical Sciences. 2022;170:106105.
36. Wang H, Wang Q, Liang C, Su M, Wang X, Li H, et al.. Acupuncture regulating gut microbiota in abdominal obese rats induced by high-fat diet. Evidence-Based Complementary and Alternative Medicine. 2019;2019.
37. Chunchai T, Thunapong W, Yasom S, Wanchai K, Eaimworawuthikul S, Metzler G, , et al. Decreased microglial activation through gut-brain axis by prebiotics, probiotics or synbiotics effectively restored cognitive function in obese-insulin resistant rats. Journal of Neuroinflammation. 2018;15(1):1-5.
38. Huang F, Zhang F, Xu D, Zhang Z, Xu F, Tao X, et al. Enterococcus faecium WEFA23 from infants lessens high-fat-diet-induced hyperlipidemia via cholesterol 7-alpha-hydroxylase gene by altering the composition of gut microbiota in rats. J Dairy Science. 2018;101(9):7757-67.
39. Sun H, Wang N, Cang Z, Zhu C, Zhao L, Nie X, et al. Modulation of microbiota-gut-brain axis by berberine resulting in improved metabolic status in high-fat diet-fed rats. Obesity Facts. 2016;9(6):365-78.
40. Kim N, Lee J, Song HS, Oh YJ, Kwon MS, Yun M, et al. Kimchi intake alleviates obesity-induced neuroinflammation by modulating the gut-brain axis. Food Research International. 2022;158:111533.
41. Wang TY, Tao SY, Wu YX, An T, Lv BH, Liu JX, et al. Quinoa Reduces High-Fat Diet-Induced Obesity in Mice via Potential Microbiota-Gut-Brain-Liver Interaction Mechanisms. Microbiology Spectrum. 2022:e00329-22.
42. Li Y, Bai D, Lu Y, Chen J, Yang H, Mu Y, et al. The crude guava polysaccharides ameliorate high-fat diet-induced obesity in mice via reshaping gut microbiota. Int J Biological Macromolecules. 2022.
43. Hu M, Zhang P, Wang R, Zhou M, Pang N, Cui X, et al. Three different types of β-glucans enhance cognition: The role of the gut-brain axis. Frontiers in Nutrition. 2022;9.
44. Guo Z, Hu B, Zhu L, Yang Y, Liu C, Liu F, et al. Microbiome-metabolomics insights into the feces of high-fat diet mice to reveal the anti-obesity effects of yak (Bos grunniens) bone collagen hydrolysates. Food Research International. 2022;156:111024.
45. Shao W, Xiao C, Yong T, Zhang Y, Hu H, Xie T, et al. A polysaccharide isolated from Ganoderma lucidum ameliorates hyperglycemia through modulating gut microbiota in type 2 diabetic mice. Int J Biological Macromolecules. 2022;197:23-38.
46. Zhou Y, Qiu W, Wang Y, Wang R, Takano T, Li X, et al. β-Elemene Suppresses Obesity-Induced Imbalance in the Microbiota-Gut-Brain Axis. Biomedicines. 2021;9(7):704.
47. Pan W, Jiang P, Zhao J, Shi H, Zhang P, Yang X, et al. β-Glucan from Lentinula edodes prevents cognitive impairments in high-fat diet-

induced obese mice: Involvement of colon-brain axis. Journal of Translational Medicine. 2021;19(1):1-7.
48. Ma X, Xiao W, Li H, Pang P, Xue F, Wan L, , et al. Metformin restores hippocampal neurogenesis and learning and memory via regulating gut microbiota in the obese mouse model. Brain, Behavior and Immunity. 2021;95:68-83.
49. Zhao L, Zhu X, Xia M, Li J, Guo AY, Zhu Y, et al. Quercetin ameliorates gut microbiota dysbiosis that drives hypothalamic damage and hepatic lipogenesis in monosodium glutamate-induced abdominal obesity. Frontiers in Nutrition. 2021;8:671353.
50. Wu J, Zhu Y, Zhou L, Lu Y, Feng T, Dai M, , et al. Parasite-derived excretory-secretory products alleviate gut microbiota dysbiosis and improve cognitive impairment induced by a high-fat diet. Frontiers in Immunology. 2021;12.
51. Yang X, Zheng M, Hao S, Shi H, Lin D, Chen X, et al.. Curdlan prevents the cognitive deficits induced by a high-fat diet in mice via the gut-brain axis. Frontiers in neuroscience. 2020;14:384.
52. Biyong EF, Alfos S, Dumetz F, Helbling JC, Aubert A, Brossaud J, et al. Dietary vitamin A supplementation prevents early obesogenic diet-induced microbiota, neuronal and cognitive alterations. International Journal of Obesity. 2021;45(3):588-98.
53. Lee S, Goodson M, Vang W, Kalanetra K, Barile D, Raybould H. 2′-fucosyllactose supplementation improves gut-brain signaling and diet-induced obese phenotype and changes the gut microbiota in high fat-fed mice. Nutrients. 2020;12(4):1003.
54. Tang T, Song J, Li J, Wang H, Zhang Y, Suo H. A synbiotic consisting of Lactobacillus plantarum S58 and hull-less barley β-glucan ameliorates lipid accumulation in mice fed with a high-fat diet by activating AMPK signaling and modulating the gut microbiota. Carbohydrate Polymers. 2020;243:116398.
55. Liu Z, Li L, Ma S, Ye J, Zhang H, Li Y, et al. S. High-dietary fiber intake alleviates antenatal obesity-induced postpartum depression: Roles of gut microbiota and microbial metabolite short-chain fatty acid involved. Journal of Agricultural and Food Chemistry. 2020;68(47):13697-710.
56. Diling C, Yinrui G, Longkai Q, Xiaocui T, Yadi L, Jiaxin F, et al. Metabolic regulation of Ganoderma lucidum extracts in high sugar and fat diet-induced obese mice by regulating the gut-brain axis. Journal of Functional Foods. 2020;65:103639.
57. Ahmadi S, Nagpal R, Wang S, Gagliano J, Kitzman DW, Soleimanian-Zad S, et al. Prebiotics from acorn and sago prevent high-fat-diet-induced insulin resistance via microbiome–gut–brain axis modulation. The Journal of Nutritional Biochemistry. 2019;67:1-3.
58. Kong C, Gao R, Yan X, Huang L, Qin H. Probiotics improve gut microbiota dysbiosis in obese mice fed a high-fat or high-sucrose diet. Nutrition. 2019;60:175-84.
59. Zhuang P, Shou Q, Lu Y, Wang G, Qiu J, Wang J, et al. Arachidonic acid sex-dependently affects obesity through linking gut microbiota-driven inflammation to hypothalamus-adipose-liver axis. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2017;1863(11):2715-26.
60. Ansari A, Bose S, Yadav MK, Wang JH, Song YK, Ko SG, et al. CST: An herbal formula, exerts anti-obesity effects through brain-gut-adipose tissue axis modulation in high-fat diet fed mice. Molecules. 2016;21(11):1522.
61. Zhou Y, Guo W, Lei L, Sun Y, Li R, Guo Y, et al. Bis (2-ethylhexyl)-tetrabromophthalate induces zebrafish obesity by altering the brain-gut axis and intestinal microbial composition. Environmental Pollution. 2021;290:118127.
62. Wen L, Duffy A. Factors influencing the gut microbiota, inflammation and type 2 diabetes. The Journal of Nutrition. 2017;147(7):1468S-75S.
63. Furman BL. Streptozotocin-induced diabetic models in mice and rats. Current Protocols. 2021;1(4):e78.
64. Rohilla A, Ali S. Alloxan induced diabetes: mechanisms and effects. Int J Res Pharmaceutical and Biomedical Sciences. 2012;3(2):819-23.