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A COMPARATIVE EVALUATION OF THE IMPACT OF HIGH FAT AND HIGH SALT DIETARY COMPONENTS ON HUMAN AND MICE GUT MICROBIOTA

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ABSTRACT

The human gut microbiota becomes a hotspot of research attention owing to its close association with human health and human diseases. The modern diet is a meal that contains high levels of refined sugar, refined grain, trans fat, and polyunsaturated fat, salt, and numerous food additives. In this pretext, the global nutrition transition from a traditional diet primarily rich in complex carbohydrates and fibre to a modern diet has provoked an alarming situation. Mouse models have been extensively used to elucidate the complex host-microbiome interplay in nutrition and diseases development. The interpretation of gut microbiome research in mouse models in the context of human milieus requires the knowledge of intrinsic similarity and difference between two systems. The large body of evidence proves that mice microbiota are similar in the context of human microbiota except for some difference that might reflect the disparities in host factors including genetic origin, diet, gender and sex. Moreover, some dissimilarity even reported by different researchers are due to limited dataset size and diversity of studies. Moreover, few published articles have also represented the change in gut microbial composition as a combination of order, family, genus and species, which confuses during the analysis of outcomes. In this review article, we

compiled the comparison of gut microbiota alteration induced by high fat and high salt dietary interventions in both hosts up to lower taxonomic levels based on published reports.

Keywords: Gut Microbiota, Classification, Murine models, High fat diet, and High salt diet

1. INTRODUCTION

The adaptation toward the modern diet provoked an alarming situation across the world. Widespread consumption of modern diet or junk food has serious adverse effects on human health **[1]**. The origin of modern western cooking can be traced back to the 17th century **[2]**. In 1972, Michael Jacobson, Director of the Center for Science, Washington DC coined the term junk food as slang in the public interest **[3]**. Junk food that is high in fat, sodium, and sugar and provides high calories has been adopted as a modern diet by the present generation **[4]**. Sproesser *et al* defined the modern diet as high consumption of meat, sugar, oils, and fats while traditional diets have been defined as a high intake of fibre and grain **[5]**. According to Statovci *et al* a diet having a high content of saturated fats, refined grains, sugar, alcohol, salt, proteins (derived from fatty domesticated and processed meats), and corn-derived fructose syrup associated with reduced consumption of fruits and vegetables would be considered as a western diet **[6]**. Although, the different terms are used for the modern consuming pattern as junk food or modern diet or western diet by the various articles they have general harmony in term of pleasurable ingredient especially the high content of fat, salt and sugar (HFSS).

1.1 High fat diet

On the basis of detailed reviewing of Indian studies, government reports and international evidence, the total fat (Visible and invisible) intake in the daily diet should be around 20-30% of total calories. Within total energy intake per day, Saturated Fatty Acids level should be less than 10%, Polyunsaturated Fatty Acids 6-10%, Trans Fatty Acids must be less than 1% and Monounsaturated Fatty Acids by difference about 5-10% **[7]**. As per national and international guidelines, the intake of fat above 35% of total energy is considered as high fat **[8, 9]**. However, the upper limit on total fats was recently revoked from the USDA guidelines (2015). Importantly, the Mediterranean diet that is considered one of the healthiest diets contains more than 35% fats (healthy fat i.e. unsaturated fats). Saturated fats and Trans fats which are major ingredient of the modern diet are bad fats.

1.2. High salt diet

As per ICMR and WHO guidelines, the added salts should be restricted to 5-6 g per day **[10]**. As per WHO guidelines, the consumption of salt above 6g/day (>2g/day sodium) would be high. However, the new WHO guideline recommended that the salt intake should be less than 5 g per day (equivalent to sodium intake of less than 2 g per day) **[11]**. Most people consume too much salt i.e. on an average 9–12 g per day, or around twice the recommended maximum level of intake **[12]**. In India, the daily intake of salt was estimated to be 8 and 9 g/d of added salt (fixed and random effects). All these values are higher than recommended intakes by the NIN, ICMR and WHO **[7]**.

1.3. Gut microbiota

Emerging priorities towards gut microbiota research have been acknowledged across the world due to their extensive involvement in health and development or progression of diseases **[13]**. The human gut microbiota is a highly complex and dynamic community dominated by the bacterial species belonging to Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria. Fusobacteria and Verrucomicrobia with two major phyla Firmicutes and Bacteroidetes which account for 90% of the gut microbiota population **[14]**. Prominently, the human gut ecosystem is not the static elements and primarily driven by various factors like host physiology, diet, antibiotics, and the interactions between individual microbes **[15]**. Widespread consumption of food that is high in fat and salts, considered as part of the modern diet or junk foods have serious adverse effects on human health and development or progression of diseases inducing the metabolic disorders, immune-related disorders and effecting of neurobehavioural traits **[1]**.

The comprehensive understanding of human microbiota can be accomplished through animal-based research only. Several studies showed the shift of gut microbiota in terms of their composition and responses upon dietary perturbations of high fat and high salt dietary components and associated disease conditions. In this reviw article, we summarize the full classification up to species level of these altered gut microbes in both hosts with their critical role in health and disease. The delineation of microbiota up to lower taxonomic levels from various peer-review articles would directly help in pinpoint the difference of shifting of gut microbiome between human and mice linking with high fat and high salt dietary products of human beings and translating the gut microbiome research results from mice models to humans.

2. HUMAN AND MICE GUT MICROBIOTA IN HEALTHY STATE

The mammalian digestive tract is highly conserved. The murine models are an indispensable and powerful tool to insight the host-microbiota interactions. However, attention is highly required in making the similarities between gut microbiota composition in mice models and humans.

The inconsistencies between the gut microbiota of two organisms were mainly due to inter-organism variations, inter-study variations and the various confounding factors including, diets, environmental conditions, exposure to pathogens and drugs **[16]**. Conversely, the recent studies indicated that the gut microbiota in mice and humans shared similarity at the genus level irrespective of their different proportions. Further, the gut microflora of mice and humans has also conferred the similarity in function **[17]**.

The gut microbiota functions like a dynamic organ and mediates several physiological, metabolic, nutritional, immunological and even neurological functions by interacting with multiple organs in the host **[18]**. They also work as a virtual endocrine organ that produces several metabolites that exert influence on host physiology by triggering the responses at both the local and distant levels **[19]**. The knowledge of core flora and their role in both species is highly essential to understand the microbial shift and their impact under different dietary perturbations. The comparison of gut microbiota of healthy mice and humans is shown in **Table 1**.

Table 1: Comparison Of Gut Microbiota Of Healthy Mice And Human

Features	Human	Mice	Refs.
Core phylum reported*	Mainly identified 12 different phyla and four major phyla are Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes shared 93.5% of the core microbiota	Identified 37 core genera which are divided into mainly five core groups	20 21
Dissimilarity in gut microbiota at the phylum level	Higher abundance of Bacteroides vs Firmicutes. Abundance of Actinobacteria and Proteobacteia The abundance of Tenericutes markedly low	Higher abundance of Firmicutes vs Bacteroides. Actinobacteria are hardly detectable Proteobacteria abundance lowest The abundance of Tenericutes markedly high	
Dissimilarity in gut microbiota at the family level	Prevotellaceae and Prevotella. Ruminococcaceae	S24-7 (and an unclassified genus of this family) Clostridial	
Dissimilarity in gut microbiota at the species level	Prevotella, Faecalibacterium & Ruminococcus	Lactobacillus, Alistipes & Turicibacter	16
The similarity in gut microbiota at the genus level	Clostridium, Bacteroides and Blautia	Clostridium, Bacteroides and Blautia	22
Exclusively gut microbiota at the species level	Faecalibacterium, Mitsuokella, Megasphera, Dialister, Asteroleplasma, Succinivibio, Sutterella, Paraprevotella and Phascolarctobacterium	Mucispirillum, Faecalibacterium	23 24
Microbiota enterotypes	Bacteroides (enterotype 1), Prevotella (enterotype 2) and Ruminococcus (enterotype 3	Lachnospiraceae/ Ruminococcaceae & Ruminococcaceae enterotype	25

*In the stomach –Helicobacter, Prevotella, Streptococcus, Veillonella, and Rothia (Actinomycetaceae)
*In small intestine- Streptococcus, Lactobacillus, Enterococcus and members of the Enterobacteriaceae family
*In large intestine- Bacteroides (enterotype 1), Prevotella (enterotype 2) or Ruminococcus (enterotype 3)

3. HIGH FAT DIETARY MODULATION OF THE MICROBIOTA IN HUMAN AND MICE

Accumulating scientific evidence implies that even the gut microbiota composition shaped by many dynamic factors including genetics, physical environment, age and stress, the contribution of diet is most significant in orchestrating the host-microbiota crosstalk onset from the beginning of life **[26]**. A consolidated body of evidence supported that most of the findings observed in mice experimentation concurred with that in human studies. Mice and human gut microbiota recorded the similarity of microbiota at the genus level. However, the different proportions of microbiota projected by various researchers **[17, 27]**. Moreover, the mouse gut microbiota is functionally similar to its human counterpart and the variation in microbial shift reflected at lower taxonomic levels **[27]**. Various reasons accounted for by different researchers, although the most outstanding explanation was that the experimental studies in mice are performed in highly controlled environments and fed specific diets **[28].** But those levels of control in human studies are not plausible; therefore, the shifts in the microbiota can be considerably more variable.

The Short-term changes in dietary patterns can impact the intestinal microbiota composition to some extent but the substantial modifications to microbiota induced by long-term changes in the diet only **[29, 30]**. Wu and co workers summarised that a short term identical diet did not influence the Bacteroides and Prevotella enterotypes. But a long-term diet, especially one comprising proteins, animal fats and carbohydrates, is strongly linked with Bacteroides and Prevotella enterotypes respectively **[29]**. Contrary, Sonnenburg and Backhed *et al* reported that short term or acute dietary change even daily variation also found to associate with substantial increases in microbial species at the genus and species level. However, the evidence for the permanent compositional shift of microbiota at the phylum level is inadequate. This finding is linked with the result confirmed by Wang and co workers that the feeding of wild mice with a chow diet can shift the Bacteroides to the Robinsoniella enterotype so quickly just within a week **[30]**.

A bounty of studies has been conducted to understand the consequence of a high-fat diet impact in mice or humanized mice models. Most of the studies confirmed the increased ratio of Firmicutes: Bacteroidetes in human **[31-35]** and mice models **[33, 36-44]** while few studies have also shown the decrease of Firmicutes: Bacteroidetes ratio in human **[40, 45, 46]** as well as in mouse models **[42, 47, 48]**. Most striking is that some studies also gaged the increase of both Firmicutes and Bacteroidetes in rodent species **[49, 50]**. The increase of Actinobacteria in humans **[32, 44]** and mice **[41, 49]** supported by most of the research works. Similarly, the increase in the relative abundance of Proteobacteria in humans **[34, 51]** and rodents **[38, 40, 42, 43, 47]** also confirmed by most of the studies except few studies which also observed the trend of decrease in humans **[45]**. Kim and co-workers **[49]** observed the most surprising finding that the proportion of Actinobacteria at phylum level was significantly associated with dietary fat content and the proportions of Firmicutes and Bacteroidetes were strongly associated with age. Crawford and co-workers **[52]** also noted that there are no significant differences between the groups of Firmicutes and Bacteroidetes ratio (calculated as a biomarker of gut dysbiosis) between chow-fed and high fat-fed groups of rodents. Further, the effect of high-fat (saturated) dietary products on gut microbiota in humans and mice at genus/ species level and their potential role are presented in **Table 2 & 3**.

4. HIGH SALT DIETARY MODULATION OF THE MICROBIOTA IN HUMAN AND MICE

High salt diet decreased the diversity and increased the Firmicutes: Bacteroidetes ratio in rodent models **[85]**. In rodents, high salt also increased the abundance of the *Erwinia* genus, the *Christensenellaceae*, and Corynebacteriaceae families and depleted the *Lactobacillus* species **[86]**. The depletion of beneficial microbiota *Lactobacillus*, *Akkermansia muciniphila* and *Bifidobacterium* also reported in humans with a high salt diet **[85]**. Further, the effect of high-salt dietary products on gut microbiota in humans and mice at genus/ species level and their potential role are presented in **Table 4 & 5**. The summary of the effect of high fat & high-salt dietary products on gut microbiota in human and mouse models are presented in **Figure 1 & 2**.

Table 2: Effect Of High-Fat On Gut Microbiota In Human And Mice At Genus/Species Level

Phylum	Human		Mice		Refs.
	Family	Genus/ Species	Family	Genus/Species	
Firmicutes	*Erysipelotrichaceae* *Clostridiaceae* *Oscillospiraceae*	↑*Erysipelotrichi* ↑*Clostridium* ↑*Oscillobacter*	*Erysipelotrichaceae* *Bacillaceae* *Clostridiaceae* *Streptococcaceae* *Enterococcaceae* *Lactobacillaceae*	↑*Allobaculum* ↑*Clostridia* ↑*Clostridium* cluster ↑*XIVa* ↑*Streptococcus* ↑*Enterococcus* ↓ ↑*Lactobacillus*	36 53-61
Bacteroidetes	*Bacteroidaceae* *Porphyromonadaceae* *Rikenellaceae*	↑*Bacteroides* ↑*Enterotypes* ↑*Barnesiella* ↑*Alistipes*	*Bacteroidaceae* *Porphyromonadaceae* *Rikenellaceae*	↑↓ *Bacteroides* ↑*Barnesiella* ↑*Alistipes*	40 55 62 63

Proteo bacteria	***Desulfovibrionaceae*** ***Desulfovibrionaceae***	**↑*Bilophila*** **↑Desulfovibrio**	***Desulfovibrionaceae*** ***Desulfovibrionaceae*** ***Enterobacteriaceae***	**↑*Bilophila*** **↑Desulfovibrio** **↑*Proteus***	**53** **56**
Actino bacteria	***The proportion of phylum increased***				**32** **41** **45** **49**
Firmi cutes	*Eubacteriaceae* ***Ruminococcaceae*** ***Lactobacillaceae*** ***Lachnospiraceae*** ***Ruminococcaceae***	**↓ *E. rectale*** **↓ *R.bromii*** **↓ *Lactobacillus*** **↓ *Roseburia*** **↓*F. prausnitzii***	***Erysipelotrichaceae*** ***Eubacteriaceae*** ***Ruminococcaceae***	**↓ *Turicibacter*** **↓ *E rectale*** **↓*Blautiacoccoides***	**37** **53** **56** **60** **64**
Bacteroi detes	***Rikenellaceae*** ***Prevotellaceae***	**↓ *Bacteroides*** **↓ *Prevotella***	***Lachnospiraceae*** ***Prevotellaceae*** ***Muribaculaceae***	**↓ *Roseburia*** **↓ *Prevotella*** **↓ *S24-7***	**47** **53** **56** **65**
Actino bacteria	***Bifidobacteriaceae***	**↓ *Bifidobacterium***	***Bifidobacteriaceae***	**↓*Bifidobacterium***	**56** **60**
Verruco microbia	***Akkermansiaceae***	**↓ *Akkermansia***	***Akkermansiaceae***	**↓ *Akkermansia***	**56** **60**
Teneri cutes			***Anaeroplasmataceae***	**↓ *Anaeroplasma***	**56** **60**

↑-Increase in number; ↓- Decrease in number; ↑↓- Positive and negative effects seen in different studies

Table 3: High-Fat Alteration Of Gut Microbiota With Their Full Taxonomic Classification And Key Functions

Phylum/ Class/ Order/Family	Genus	Species	Function	Refs.
Actinobacteria *Coriobacteria* *Bifidobacteriales* *Bifidobacteriaceae*	*Bifido bacterium*	*B. longum*	Produce Short-chain fatty acids, folate, vitamin K, riboflavin, biotin, and nicotinic acid. Increases gut barrier integrity.	66
		B .bifidum	Activate the host immunity, and metabolize host glycans such as mucin.	67
		B. adolescent	Increase folate concentration & Regulatory T cells (Treg) response.	68
Firmicutes *Clostridia* *Clostridiales* *Clostridiaceae*	*Clostri dium*	*Clostridium spp.*	Maintain normal intestinal structure and physiology by producing butyrate.	36
		C. difficile	Produces toxins cause severe intestinal inflammation, diarrhoea, and colitis.	69
Firmicutes *Clostridia* *Clostridiales* *Lachnospiraceae* Eubacteriaceae	*Roseburia*	*R.intestinalis & R. hominis*	Control of gut inflammatory & maturation of the immune system, through the production of butyrate.	69
	Blautia		Produces butyric acid and acetic acid.	71
	Eubac terium	*E. rectale*	Produce butyrate in the colon.	27
Firmicutes *Erysipelotrichia* *Erysipelotrichales* *Erysipelotrichaceae*			Host lipid metabolism, inflammation and highly immunogenic.	72
Firmicutes *Bacilli* *Lactobacillales* *Lactobacillaceae*	*Lacto bacillus*	*L. reuteri*	Increases expression of Occludin (OCLN) and tight junction protein 1 (TJP1)	73
		L.plantarum	Promoting epithelial integrity by increasing Intestinal epithelial cells (IEC).	74
Firmicutes *Bacilli* *Lactobacillales* *Streptococcaceae*	*Strepto coccus*		Produce fermentation of sugars and yielding lactic acid.	75
Firmicutes *Bacilli* *Lactobacillales* *Enterococcaceae*	*Entero coccus*	*E. faecium*	Inflammation by altering the composition of bile acids.	76

Bacteroidetes Bacteroidia Bacteroidales Bacteroidaceae	***Bacteroides***	***B. vulgatus***	**Decreases gut colonization of enterobacteriaceae.**	**77**
		B. thetaiotaomicron	**Mucin degrades by foraging on O-glycans and produce SCFAs.**	**78**
		B. fragilis	**Induces the differentiation of Treg cells, promoting host immune development.**	**79**
Porphyrmonadacee	***Barnesiella***	***B. intestinilis hominis***	**Enhanced cognate anticancer immune responses.**	**80**
Rikenellaceae	***Alistipes***	***A. finegoldii***	**Cell cycle regulation of colon epithelium and leading to epithelial and tumour cell proliferation.**	**62**
Prevotellaceae	***Prevotella***	***Prevotella***	**Produce butyrate.**	**37**
Proteobacteria Delta Proteobacteria Desulfovibrionales Desulfovibrionaceae	***Desulfovibrio***	***D.intestinalis***	**Increase H2S, toxic product production. Decrease butyrate, Immune system (Th1) disruption.**	**81**

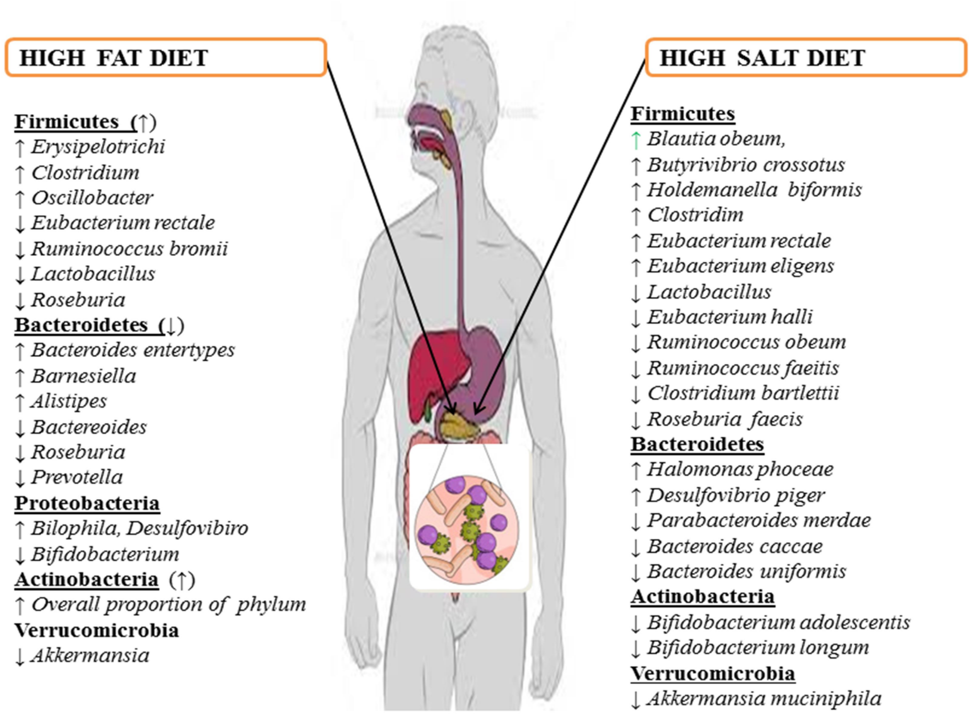
Table 4: Effect of High-Salt on Gut Microbiota in Human and Mice at Genus/Species Level

Phylum	**Human**		**Mice**		**Refs.**
	Family	**Genus/Species**	**Family**	**Genus/Species**	
Firmicutes	*Lachnospiraceae* **Lachnospiraceae** *Erysipelotrichaceae* *Clostridiaceae* **Eubacteriaceae**	*↑Blautiaobeum* *↑Butyrivibrio crossotus* *↑Holdemanella biformis* *↑Clostridium* *↑Eubacterium rectale* *↑Eubacterium eligens*	*Lachnospiraceae* *Oscillospiraceae* *Oscillospiraceae* *Ruminococcaceae* *Christensenellaceae*	*↑Roseburia* *↑Oscillibacter* *↑Oscillospira* *↑Ruminococcus*	**82** **83** **84** **85** **86**
Proteobacteria	*Halomonadaceae* *Desulfovibrionaceae*	*↑Halomonas phocaea* *↑Desulfovibrio piger*	*Sutterellaceae* *Enterobacteriaceae*	*↑Parasutterella* *↑Erwinia*	**84** **86**
Actinobacteria			*↑Corynebacteriaceae*		**84**
Verrucomicrobia			*Verrucomicrobiaceae*	*↑Akkermansia*	**86**
Decrease of microbiota					
Firmicutes	*Lactobacillaceae* *Eubacteriaceae* *Ruminococcaceae* *Ruminococcaceae* *Lachnospiraceae* *Lachnospiraceae*	*↓Lactobacillus* *↓Eubacteriumhallii* *↓Ruminococcus obeum* *↓Ruminococcus faeitis* *↓Clostridium bartlettii* *↓Roseburiafaecis*	*Lactobacillaceae* *Lactobacillaceae* *Lachnospiraceae* *Lachnospiraceae* *Lachnospiraceae* *Oscillospiraceae* *Ruminococcaceae* *Pseudoflavonifractor*	*↓Lactobacillus* *↓Lactobacillus murinus* *↓Anaerostipes* *↓Clostridium XIVa* *↓Johnsonella* *↓Oscillibacter*	**83** **84** **85** **86**
Bacteroidetes	*Porphyromonadaceae* *Bacteroidaceae* *Bacteroidaceae*	*↓Parabacteroides merdae* *↓Bacteroides caccae* *↓Bacteroides uniformis*	*Rikenellaceae* *S24-7*	*↓Alistipes*	**86**
Actinobacteria	*Bifidobacteriaceae*	*↓Bifidobacterium adolescentis* *↓Bifidobacterium longum*	*Micrococcaceae*	*↓Rothia*	**83** **86**
Verrucomicrobia	*Verrucomicrobiaceae*	*↓Akkermansia muciniphila*			**83**

↑-Increase in number; ↓- Decrease in number;

Table 5: High Salt Alteration of Gut Microbiota With Their Full Taxonomic Classification and Key Functions

Phylum/ Class/ Order/Family	Genus	Species	Function	Refs.
Actinobacteria Actinobacteria Actinomycetales Corynebacteriaceae	*Coryne bactrim*	*C.botulinum*	Cause infant diarrhoea	87
		C. difficile	Produce toxin associated with gastrointestinal illness.	88
		C.coccoides	Production of Short-chain fatty acids (SCFAs) used as fuel for the host's colonocyte.	87
Firmicutes Clostridia Clostridiales Clostridiaceae	*Oscillospiraceae*	*Oscillobacter*	Decreases expression of tight junction protein 1(TJP1).	89
Firmicutes Clostridia Clostridiales Lachnospiraceae	*Anaero Stips*	*Anaerostipes*	Produce butyrate from lactate.	90
Firmicutes Clostridia Clostridiales Ruminococcaceae	*Rumino coccus*	*R. faecis*	Produce butyrate by the degradation of resistant starch in the colon.	90
		R. gnavus	Remodelling of mucin glycosylation and adaptation of gut commensal bacteria to the mucosal niche.	91
		R. callidus	Produce butyrate by degrading starch &xylan.	92
Bacteroidetes Bacteroidia Bacteroidales Tannerellaceae	*Para bacteroides*	*P. distasonis*	Alleviate metabolomics dysfunction by the production of succinate and secondary bile acids.	93
Verrucomicrobia Verrucomicrobe Verrucomicrobials Akkermansiaceae	*Akkermansia*	*A.muciniphila*	Mucin degrading specialist & increases goblet cell (GC) mucus and intestinal epithelial cell (IEC) TJ (Tight junction) protein synthesis.	94



↑-Increase in number; ↓- Decrease in number

Fig. 1. Impact of the high fat & high salt in human gut microbiota composition

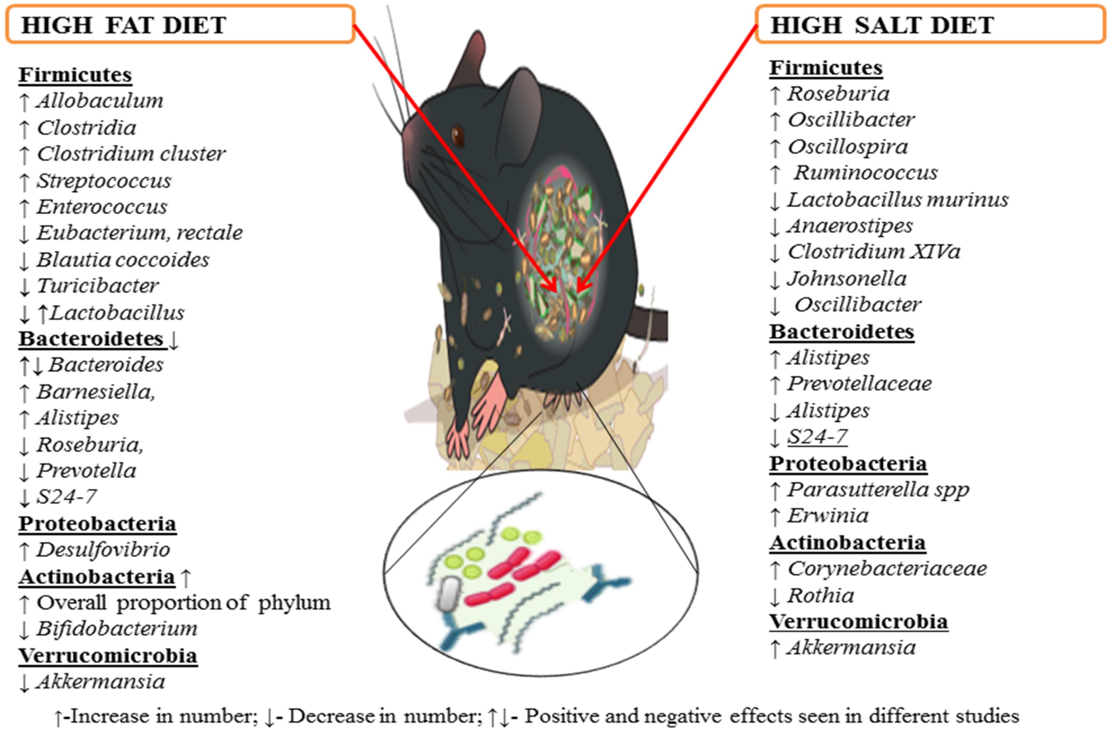


Fig. 2. Impact of high fat & high salt in mouse gut microbiota composition.

5. CONCLUSION

The rodent models will certainly help us a platform to study the role of diet nutrition and their effects of the microbiome for many diseases in humans. The review benefits us to elucidate the impact of dietary products and change in the microbiota. Based on many published reports, it represents the variation in the gut microbes on a particular diet between mice and human beings. Investigators working on mice models and who want to translate the effects of high fats and salt on gut microbiota or for the investigation of any chronic diseases should discreetly consider the shifts in changes for better reproducibility and translational application. Many studies supported that even humanized mice were not more reliable predictors of human diet than conventional mice, but this may be due to considerable technical and experimental differences across studies rather than a reflection of the underlying physiology. In the wake of some controversy existing with the current animal models of gut microbiota and reporting of differences in gut microbial changes in perturbation with high fat and high salt dietary products still a source of confusion. However, there is still a higher need to develop further promising rodent models which closely reflect the gut milieu of humans. Finally, this article will help the researchers in short out of discrepancies in terms of microbiota fingerprints for various human diseases as reported by many investigators.

Conflict of Interest

The authors wish to declare no conflict of interest.

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