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Systematic Review

Optimizing Cardiovascular Outcome in Type 2 Diabetes Mellitus with Better Control of Diabetes Mellitus with Empigliflozin and Hypertension with Renin Angiotensin System Inhibitors and Manidipine Preferably of the Dihydropyridones

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ABSTRACT

Aim: Obesity is increasing globally by leaps and bounds and thus the incidence of type 2 diabetes mellitus (T2DM) along with it so much so that the term diabesity had to be coined. Earlier we had reviewed how to treat the both together and the role of empagliflozin to improve cardiovascular outcome trials (CVOT). Similarly T2DM and hypertension are pathophysiologically-related diseases which co-exist with a broader complex of metabolic diseases which co-exist possessing similar set of risk factors. Hence it is important to consider which antihypertensives are suitable that possess a positive effect on metabolic factors in cases of T2DM who require an antihypertensive.

Method: A systematic review was carried out using the PubMed search engine with the MeSH terms: "T2DM"; "essential hypertension; "cardiovascular (CV)"; "Complications of diabetes mellitus (DM) and antihypertensive"; "Antihypertensive preferred in T2DM subjects"; "Renin-angiotensin–aldosterone system inhibitors"; "Angiotensin converting enzyme inhibitors (ACEi)"; "Angiotensin receptor blockers (ARBs)"; "Dihydropyridine calcium channel blocker"; "β2 blockers"; "Diuretics".

Discussion: Most diabetes mellitus (DM) subjects need a minimum of two antihypertensive drugs, combining a renin-angiotensin-aldosterone system (RAS) inhibitor with a dihydropyridine calcium channel blocker seems to be the most indicated approach. But not all dihydropyridine calcium channel blockers have equivalent effects on metabolic parameters. Hence manidipine that causes positive effect on insulin resistance (IR) seems to be an effective option. We have reviewed how manidipine is superior to amlodipine with regards to improving IR, not seen with amlodipine, along with not causing excessive sympathetic nervous system (SNS) activation, pulse pressure and ankle edema or to much lesser extent than amlodipine. Therefore, manidipine needs to be the first addition to RAS inhibitors in case of DM's having hypertension of the dihydropyridines calcium channel blockers. Further good blood pressure (BP) control been correlated with good CVs outcomes.

Conclusion: A RAS inhibitor is the first line of choice of drugs in a subject with T2DM who needs to be treated with empagliflozin for better CVOT outcome, and when a 2nd drug has to be added it is manidipine that is preferred over amlodipine. Plant products are proving to be having a lot of beneficial effects in DM, obesity and hypertension. Thus need for developing agents from plants will prove to be more cost effective in these chronic diseases where compliance is difficult to achieve with the use of common antiDM drugs and antihypertensives with the cost factor along with their side effects.

Keywords
Type 2 diabetes mellitus (T2DM); Diabesity; Antihypertensives; Renin-angiotensin-aldosterone system (RAS) inhibitor; dihydropyridines calcium channel blockers; Plant products.

INTRODUCTION

With increasing obesity there is simultaneous rise in co-morbidities like diabetes mellitus (DM) and hypertension (HTN), the commonest causes of cardiovascular diseases (CVD). While DM has more than 2-3 times increase in the incidence of ischemic heart disease in men than in women. The relative risk for CVD morbidity and mortality in adults with diabetes ranges from 1 to 3 in men and from 2 to 5 in women compared to those without DM as per Rivellese et al.[1,2] Other than DM, it has been seen that roughly 54% of stroke, 47% cases relating to coronary artery disease, with roughly 14% of mortality globally is attributed to arterial hypertension.[3] Analysis of data related to 11 researches involving 28,887 people between 35-74-years got included in which total prevalence of hypertension turned out to be 47% in men and 39% in women, and of DM 16% and 11% respectively.[4] Since instance of obesity are rising out of proportion and although only 171 million people having DM in 2000, the rough calculation for 2030 is 350 million.[5]

Between DM and hypertension a close association gets reflected by patients presenting with DM have a doubling of chance of hypertension, and conversely those individuals who had hypertension had a 2.5 times chance of developing DM.[6] Thus over 60% patients with DM have hypertension and with the acquisition of albuminuria incidence of hypertension goes up to 90%.[6] Further in patients of DM roughly 75% of cardiovascular system (CVS) outcomes are associated with hypertension.[1,7] On the presence of both further risk of CVS complications especially Coronary heart disease (CHD).[8] Hence controlling the risk factors control targets that is recommended in DM is the best method of preventing CVS risk in T2DM patients.[9]

Earlier we have concentrated on etiopathogenesis of obesity, ways of improving medical management of obesity over bariatric surgery, considering diabesity together for management of obesity and DM. This article is a review of how to effectively manage hypertension an important complication of obesity, that has an effect on cardiovascular outcome trials (CVOT) outcome of antidiabetic therapies[10-19] and further the advantages and role of manidipine over amlodipine addition to a renin-angiotensin–aldosterone system inhibitor is considered in detail.

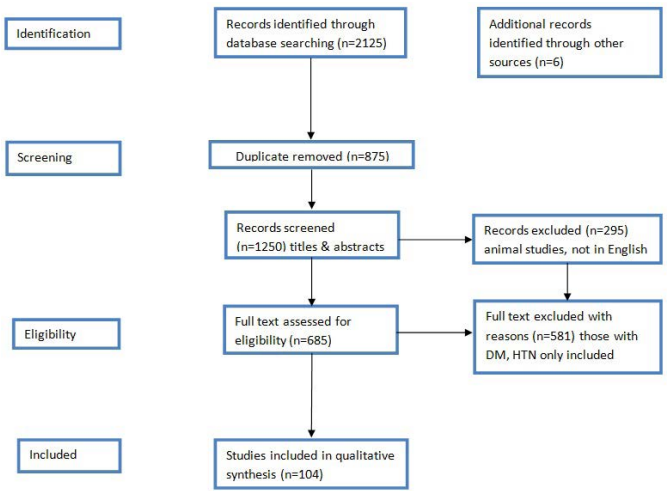
METHODS

A systematic review was carried out using the PubMed search engine with the MeSH terms: "T2DM"; "essential hypertension; "cardiovascular (CV)"; Complications of DM and antihypertensives"; "Antihypertensives preferred in T2DM Subjects"; "Renin-angiotensin-aldosterone system inhibitors"; "Angiotensin converting enzyme inhibitors (ACEi)"; "Angiotensin receptor blockers (ARBs)"; "Dihydropyridine calcium channel blocker"; "β2 blockers"; "Diuretics".

RESULTS

We found a total of 2131 articles out of which we selected 104 articles for this review. No meta-analysis was done. The articles chosen emphasized on treatment of obese subjects having both T2DM as well as hypertension (Figure 1).

Figure 1. *Overview of Literature Search with Inclusion Criteria*



n=number; DM-Diabetes mellitus; HTN-Hypertension

CAUSES OF HYPERTENSION IN DM

Of the multiple explanations given i) increased activation of the renin-angiotensin–aldosterone, ii) the sympathetic nervous system (SNS), iii) oxidative stress, iv) low-grade inflammation status and v) changes in the insulin–stimulated vasodilation, vi) impairment of innate and adaptive immunity, vii) abnormal processing of sodium by kidney viii) along with presence of nephropathy have been involved in causing both hypertension and DM.[20] How many of these factors operate in an isolated patient differs between subjects although all of these may contribute to the change in homeostatics of the patient.[20-22] Further the increase in adipose tissue (AT) and obesity have an impact on etiopathogenesis of DM and hypertension. The chronic low-grade inflammations, along with oxidative stress present in AT of obese subjects stimulate the activation of renin-angiotensin–aldosterone system.[10-13] Further viii) leptin that is an adipokine that is synthesized by AT is elevated in obese individuals, that stimulates the SNS.[20]

There is 50% presence of insulin resistance (IR) in hypertensive patients that causes damage to the vessels, which includes abnormal function, stiffness of vessels, hypertrophy, fibrosis and remodeling. Additionally, IR increases sympathetic output and aids in sodium reabsorption in the diluting segment of the distal nephron, causing reduced sodium excretion and ultimately higher blood pressure (BP) levels. Further IR also promotes renin-angiotensin-aldosterone system. Higher insulin volume along with sodium retention in the kidney along with activation of the SNS.[20-23] Conversely oxidative stress because of reactive oxygen species (ROS) synthesis helps in the development of further IR, DM along with hypertension.[20,23]

Activation of SNS is seen in cases of essential hypertension and DM. Though lot of factors are responsible for this,

like genetic influence, increased salt intake, sedentary lifestyle, with obesity being an important factor. Obesity helps in SNS activation *via* a lot of modes like i) increased–sodium–intake–associated methods, ii) cardiopulmonary reflex function abnormality, iii) renin-angiotensin–aldosterone system activation, iv) baroreflex abnormal function, v) chemoreceptor function abnormalities, vi) central factors, vii) changes in insulin, leptin amounts or ix) ROS, x) Nitric Oxide (NO) balance problems. This abnormality in the balance might get partly resolved by chronic intake of certain long acting dihydropyridine calcium channel blockers.[21,24-26] Increased platelet aggregation, with presence of abnormal balance between coagulation and fibrinolysis are other factors attributed to the procoagulant state that has been demonstrated in subjects of DM and hypertension.[2,20,21]

Use of Antihypertensive Agents in Subjects with T2DM and Hypertension

As per the United Kingdom Prospective Diabetes Study (UKPDS) in T2DM, it was demonstrated that once 10 mmHg systolic blood pressure (BP) reduced, a decrease in complications of DM by 12% (p<0.0001), decrease in mortality related to DM by 15% (p<0.0001), with microvascular side effects by 13% (p<0.0001), reduced myocardial infarction (MI) by 11% (p<0.0001). What was important was that decreasing BP had more benefits with regard to CVS events than glycaemic control per se.[27]

Although the observational studies have indicated that the lesser, the better for BP in DM, only benefits seen on macro and microvascular side effects once decrease BP upto <140/90 mmHg in DM as per randomized controlled trials (RCTs). Moreover in certain high-risk hypertensive patients with DM, increased fall in BP might cause harm.[28] Like in ACCORD (Action to Control Cardiovascular in DM trial), where 4,733 subjects with T2DM got randomized to a systolic BP goal <120 mmHg (intensive therapy) or <140 mmHg (standard therapy), the risk for the primary outcome was same in both groups following a mean follow-up of 4.7-years. But aggressive therapy was correlated with decreased risk of stroke (HR 0.59; 95% CI 0.39-0.89), but with increased risk of serious side effects secondary to antihypertensive agents.[29] Lower total mortality risk (RR 0.73; 95% CI 0.53-1.01), was observed in another study that evaluated 5 clinical trials, where decrease of BP (128/76 *vs* 135/83 mmHg) in cases of DM was achieved.[30] In view of that the BP targets have been reconsidered in patients with both DM and hypertension.[28] Thus in contrast to the earlier recommendations of BP < 130/80 mmHg for diabetics, recent recommendations are a BP target of <140/85 mmHg (European Society of Hypertension/European Society of Cardiology) or <140/90 mmHg (Eigth Joint National Committee and American Society of Hypertension/International Society of Hypertension.[31,32] Contrary to that epidemiological studies have revealed that though the last year BP control has become better, the actual fact is that a less number of subjects having hypertension and DM do not achieve BP goals at present.[33]

Though all first line antihypertensive drugs decrease BP similarly, and thus can be used in DM, it has been seen that renin-angiotensin–aldosterone system inhibitors give added benefits on both CVS along with renal outcomes beyond only BP regulation in these subjects.[26-28] Meta-analysis carried on 10 RCT studies having a total of 21,871 subjects with hypertension and T2DM which evaluated the effects of Angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) on CVS events demonstrated that the total treatment with ACEi/ARBs markedly decreased the risk of CVS events by 10% and risk of CVS deaths by 17%.[34]

Further therapy using ACEi/ARBs has been observed to help in avoiding or minimal delay the formation of nephropathy in subjects with T2DM. Hence in a meta-analysis comprising of 28 studies, where 18 studies ACEi/ARBs *vs* active drugs, 31 comparisons and 13 studies compared ACEi/ARBs *vs* placebo, 20 comparisons as compared to other antihypertensives, inspite of similar decreases in BP, therapy with ACEi/ARBs was correlated with marked reduction in risk of serum creatinine doubling along with macroalbuminurea. Further the number of patients who demonstrated albuminurea disappearance were more in patients treated with ACEi/ARBs. Additionally a lesser chance of end-stage renal disease and microalbuminuria was seen in the ACEi/ARBs group.[35] But use of ACEi or ARBs is of special use, various clinical trials have shown combining the two needs to be avoided, as no benefit is seen with more chance of side effects.[36] Hence unless contraindicated every subject with T2DM with hypertension should be treated with a ACEi or an ARB.[31,32]

Nevertheless it has been shown that approximately 75% of subjects of T2DM with hypertension will need a minimum of 2 antihypertensives for attaining the BP target.[33-36] Earlier traditions involved in maximum cases use of a renin-angiotensin–aldosterone system inhibitor along with a thiazide–like diuretic or a calcium channel blocker. But avoiding cardiovascular events in combination therapy in patients living with systolic hypetension (ACCOMPLISH) trial demonstrated in 11,506 subjects who were high-risk hypertensives that combination of an ACEi with a dihydropyridine calcium blocker decreased the risk of CVS events when compared with ACEi along with a hydrochlorothiazide.[37] These results were counter checked in the subgroup of patients having T2DM. Hence in this subgroup in contrast to hydrochlorothiazide group the combination with the calcium blocker decreased the risk of CVS death, MI, stroke, hospitalization secondary to angina, resuscitated arrest and coronary revascularization by 21% (HR 0.79; 95% CI 0.68-0.92, p=0.03). Importantly coronary events along with revascularization were decreased in those subjects treated with ACEi with a dihydropyridine calcium blocker.[38] Thus if combined therapy needed for treating T2DM with hypertension, a combination of renin-angiotensin–aldosterone system inhibitor with a dihydropyridine calcium blocker needs to be given preference.

Calcium Channel Blockers in T2DM with Hypertension

In all calcium channel blockers decrease BP with efficacy, and tolerated well. They get used for T2DM with hypertension with great frequency. Like in Reduction of Endpoints in NIDDM with

the Angiotensin II Antagonist Losartan (RENAAL) study, where 1,513 subjects with T2DM and nephropathy got randomized for losartan/placebo besides receiving conventional antihypertensives, approximately 80% of patients in both groups were given calcium channel blockers for getting the BP targets.[39]

Most of the studies have evaluated the actions of calcium channel blockers on CVS outcomes in subjects with T2DM with hypertension. In the appropriate blood pressure control in diabetes (ABCD) study, as compared with enalapril, therapy with nisoldipine, correlated with markedly there are more chances of fatal along with non-fatal MI, of these patients who were cases of non-insulin DM and hypertension.[40] In case of fosinopril *versus* amlodipine cardiovascular events randomized trial (FACET) study, although BP got decreased to the same amount, with no variations in total serum cholesterol, high-density lipoprotein (HDL) cholesterol, hemoglobin A1C (HbA1c), fasting serum glucose or plasma insulin between groups, those subjects who were randomized for receiving fosinopril had significantly reduced chances of any major vascular problems, in contrast to those getting amlodipine in cases of non-insulin DM and hypertension.[41] Conversely in irebesartan diabetic nephropathy trial (IBNT), where 1,715 adult subjects having diabetic nephropathy and hypertension were randomized for getting irebesartan, amlodipine or placebo besides receiving conventional antihypertensives, time till CV death, MI, congestive heart failure (CHF), strokes and coronary revascularization happened similarly in the 3 groups. But in those getting amlodipine showed significantly decreased rate of MI as compared to placebo (HR 0.58; 95% CI 0.37-0.92; p=0.02).[42] In the huge subgroup of subjects with DM (n=5137) that were included in the BP decreasing arm of anglo-scandinavian cardiac outcome trial (ASCOT) study those getting amlodipine based therapy (where perindropil addition could be done if needed) correlated with a decrease in the incidence of the composite endpoint of total CVS events along with procedures, as compared with atenolol based regimen (thiazide could be given if needed) (HR 0.86 95% CI 0.76-0.98; p=0.026). Additionally, amlodipine based therapy was correlated with decrease in fatal and non-fatal strokes, peripheral arterial disease (PAD), and noncoronary revascularization.[43]

From these data it is clarified that although renin-angiotensin–aldosterone system inhibitors need to be considered to be the 1st line therapy for treating subjects who were cases of DM and hypertension, when a 2nd antihypertensive is needed for achieving BP control, it needs a calcium channel blocker with a renin-angiotensin–aldosterone system inhibitor has been demonstrated to be possessing complementary modes of action which increase their efficacy, with low chance of side effects.[2,44]

Role of Metabolic Control in T2DM with Hypertension

For CVS risk reduction in all in cases of DM, best method is the comprehensive management of all CV risk factors. But some antihypertensives might cause effects on metabolic parameters that are not favourable and need to be used only when the indication is very high, and are avoidable in subjects of DM or at risk of developing DM, like patients having metabolic equivalents (METs). In contrast those anthypertensives displaying a neutral/favourable metabolic parameters are the ones required to be used in such subjects preferably.[2,45]

As per many works renin-angiotensin–aldosterone system inhibitors display good effects on the glucose homeostasis. In a meta-analysis, that evaluated the actions of renin-angiotensin–aldosterone system inhibitors on the chances of new onset DM, 10 RCTs (8 regarding hypertensive population and 2 in heart failure patients) were the inclusion criteria. While 7.4% of patients getting ACEi or an ARB, had showed new onset DM, that happened in 9.63% of controls (relative risk reduction 22%; 95% CI 18-26%; p<0.00001). This effect that was of benefit was same irrespective of the type of renin-angiotensin–aldosterone system inhibitor utilized (ACEi or an ARB), the type of comparison drugs (placebo or beta blockers/diuretics or amlodipine) or the king of basic condition (hypertension, heart failure).[46] In another recent meta-analysis it has been demonstrated that ACEi decreases the chances of new onset DM in comparison with beta blockers/diuretics by 22% and with calcium channel blockers by 15%.[47] Same group observed in another meta-analysis, a reduction in new onset DM with use of ARB as compared with beta blockers/diuretics by 27%, and placebo by 12% and with calcium channel blockers by 24%.[48] This data is not astonishing in view of renin-angiotensin–aldosterone system having a crucial part in the etiopathogenesis of both hypertension and metabolism of glucose.[45]

Into a calcium channel blockers possess a neutral effect on metabolism of glucose. Hence a meta-analysis of 10 RCT, in which 108,118 hypertensive subjects with preexisting DM, calcium channel blockers correlated with a increases the chance of DM in contrast to ACEi or ARB, but with lesser chance in comparison with beta blockers/diuretics.[49] Same results have been obtained from other meta-analysis.[50] Yet not all calcium channel blockers possess the same effects on metabolism of glucose, like some researchers demonstrated azelnidipine could abrogate IR.[51] But the results got from manidipine on benefitting in IR have more consistency.[52,53]

In contrast, in aggregate, beta blockers/diuretics are shown to possess unrewarding results as far as glucose homeostasis is concerned.[48] Actually various studies have demonstrated that therapy with beta blockers causes higher chances of DM development. A Meta-analysis involving 94,492 subjects with hypertension getting therapy with, beta blockers, enhanced risk of new onset DM by 22% (RR 1.22, 95% CI 1.12-1.33) in comparison to non-diuretic antihypertensives. Risk of DM was increased with atenolol.[54] But not all beta blockers are harmful with regard to glucose homeostasis. Most of the studies have revealed that beta blockers like bisopropol, carvedilol or nebiviol might not affect glucose homeostasis in a negative way.[55]

All over the world diuretics enhance the risk of new onset DM. Hence in a meta-analysis, where 48 randomized groups out of 22 clinical trials that involved 143,153 subjects, not having DM at the time of randomization, the chance of DM with antihypertensives was least ARB and ACEi followed with calcium channel blockers and placebo beta blockers and diuretics in this

order.[56] But just like with beta blockers, all diuretics don't have the similar effect on glucose homeostasis. Hence it appears possibly chlorthalidone's metabolic profile might be helpful in contrast to other thiazide or thiazide like diuretics.[45,57] Other workers revealed that amiloride and hydrochlorothiazide decreased BP to a similar amount, therapy with hydrochlorothiazide was related to escalation of glucose levels following a 2-hours glucose tolerance test but not with amiloride.[58] In case of eplerenone in mild patients hospitalization and survival study in heart failure (EMPHASIS-HF) study tried to evaluate the efficacy of Eplerenone along with conventional therapy on clinical results in 2,737 subjects with systolic heart failure and mild symptoms in those subjects with DM at baseline (n=1846), Eplerenone did not enhance the chances of new onset DM (HR 0.94, 95% CI 9.59-1.52).[59]

Arterial Hypertension and Adrenergic Tone

In the pathophysiology of hypertension, along with metabolic control SNS plays a crucial role. Chronically enhanced sympathetic tone helps in increasing formation of obesity, hyperglycemia, IR and hypertension.[21,24,60] Further escalated sympathetic activation system might enhance pulse pressure. Its relevance is demonstrated by poor correlation of more than than pulse pressure with worst CVS prognosis is seen.[61]

First development of dihydropyridine calcium channel blockers had the characteristic of rapid release, and short lifetime, with rapid absorption. Hence tachycardia with sympathetic activation was prevalent. In contrast last generation of dihydropyridines have the properties of long life and thus prolonged action, resulting in low sympathetic activation. Hence these latter drugs possess better CVS along with tolerability profiles.[52,53] Inspite of this it is not that all 3rd generation dihydropyridine calcium channel blockers have similar action on sympathetic activation.[62,63]

Further Benefits of Manidipine on BP Control

A third generation dihydropyridine calcium channel blocker, manidipine reduces BP levels with a maintainance of effect over 24-hours, without any significant hydroxyethylrutosides (HR) rise or cardiac output increase.[64] Variety of studies have evaluated the antihypertensive efficacy of manidipine.[62,63,65-70] As per these studies manidipine decreases levels of BP in an equivalent way to enalapril, lisinolipril, or amlodipine, of the other antihypertensives. Hence in a study carried out in T2DM and hypertension, following 24-hours of therapy 10 mg manidipine and 10 mg enalapril decreased BP levels equally (-23/-13 and -20/-12 mmHg, respectively. $p<0.01$ *vs* baseline; p=NS between groups.[65] A European randomized double blind, multicentre and parallel group (MAISH) study had 195 subjects ≥60-years-old, having isolated systolic hypertension got manidipine 10-20 mg once daily or amlodipine 5-10 mg once daily. Chlorthalidone 25 mg once daily could be added in case of uncontrolled BP inspite of high dose manidipine or amlodipine therapy. Following 12-weeks of therapy same decreases in systolic BP got seen in both groups (-19.5 and-18.4 mmHg, respectively; p=NS). Another meta-analysis that included 4 RCT's head to head of minimum 12-months of therapy that compared the effectiveness of 20 mg manidipine with that of 10 mg amlodipine therapy, 838 subjects got evaluated (for 20 mg manidipine group (n=436), for amlodipine group (n=402). An equivalent antihypertensive efficacy was observed for both (for diastolic BP effect size=-0.08 and for systolic BP=-0.01(p=NS for both systolic and diastolic BP).[69] From all the above results, it is clear that as monotherapy manidipine is efficacious. But many studies have illustrated that manidipine could be utilized as add on therapy, especially to renin-angiotensin–aldosterone system inhibitors. Hence in non-comparative along with open label study 136 subjects having T2DM with unregulated hypertension inspite of combined low dose diuretic with ACEi or ARB, supplementation of manidipine 10-20 mg/day decreased BP by roughly -22/-9 mmHg ($p<0.001$) following 6-months of therapy.[71]

A common side effect of DM and hypertension is microalbuminurea. Importance of this lies in the marked correlation of microalbuminurea with higher CVS risk.[31] Decreasing BP to recommended goals is essential for decrease of urine albumin excretion rates, some antihypertensives have revealed more benefits that goes further than only BP regulation. Related to this ACEi or ARB, and not both at the same time, remain the drugs preferred for treating patients with DM and hypertension, especially those presenting with microalbuminurea.[31,32] Comparison of combination of benazepril with hydrochlorothiazide in the ACCOMPLISH trial demonstrated that the earlier antihypertensive therapy using benazepril with amlodipine reduced the progression of of manidipine nephropathy to a higher amount.[72] This matches the results of a study demonstrated in a hypertensive group of subjects having DM microalbuminurea along with unregulated BP inspite of therapy with candesartan, where in comparison to adding hydrochlorothiazide 12.5 mg/day further addition 10 mg/day decreased urine albumin excretion rates upto a higher rate inspite of similar BP decrease.[69]

But importantly not all calcium channel blockers provide the similar renal protection. The situation is, as per variety of studies in hypertension with or without DM, that manidipine results in greater renal protection, in comparison to amlodipine, inspite of equivalent BP decrease, either alone or in addition to renin-angiotensin-aldosterone system inhibitors.[62,63] Hence evaluation of AMANDHA study utilizing multivariate analysis, the treatment that had been compared (manidipine *vis-a-vis* amlodipine) showed an independent correlation with alterations in urine albumin excretion.[73] These variations get understood by that amlodipine blocks only L-type calcium channels, while manidipine blocks both L- and T-type calcium channels. L-type receptors are only situated in the afferent arterioles but not in efferent arterioles. Hence on blocking L-type calcium channels, vasodilation gets limited to afferent arterioles, which ends in glomerular hypertension and hence as a result increased urine albumin excretion. In comparison T-type calcium channels being present in both afferent and efferent arterioles, blocking these receptors ≥ vasodilation of both arterioles, thus causing a decrease in intraglomerular pressure and hence decreased urine albumin excretion rates.[62,74-76]

The most common adverse effect of dihydropyridones is ankle oedema. Cause of ankle oedema with dihydropyridones calcium channel blockers, is a rise in intracapillary pressure, because

of selective enhancement of postcapillary tone due to sympathetic activation. As not all calcium channel blockers have similar action causing sympathetic activation, risk of ankle oedema might differ between a variety of dihydropyridones. Thus a meta-analysis, where amlodipine was compared with manidipine, a 65% lower risk of development of ankle oedema (RR 0.35; 95% CI 0.23-0.54; risk difference 11.3; 95% CI 7-16%) was there. Further as renin-angiotensin–aldosterone system inhibitors dilate the arteriolar vascular bed and venous capacitance vessels, that cause a decrease in intracapillary pressure, adding renin-angiotensin–aldosterone system inhibitors with dihydropyridones calcium channel blockers might decrease the ankle oedema related to dihydropyridones.[44,62] Hence in a study which included patients with untreated hypertension, adding delapril to manidipine, in part had a counter effect on the microcirculatory effects caused by manidipine that led to oedema. In this 3-way crossover study, in 3 subjects clinically appreciable ankle oedema were following manidipine monotherapy, and 1 patient with the combination of delapril and manidipine.[68]

Metabolic Effects of Manidipine

Several studies have pointed that manidipine improves insulin sensitivity by helping in the development along with differentiation of adipocytes, along with retaining peroxisome proliferator-activated receptor-gamma (PPAR-γ) action.[52,53,77] These have been demonstrated with manidipine in both when used as monotherapy, along with use in combination with renin-angiotensin–aldosterone system inhibitors.

Evaluation of metabolic effects of 10 to 20 mg manidipine once daily for 12-weeks was carried out in an open label and non-comparative study demonstrated in 102 cases of stage I-II essential hypertension from both sexes. No changes in metabolic parameters like fasting plasma glucose, total high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, triglycerides along with insulin sensitivity index was observed significantly.[78] Another study conducted in hypertensive subjects ≥ 70-years, therapy with manidipine for 6-months was not correlated with changes in glucose or lipid parameters, though a pattern of decreased triglycerides levels was seen.[79]

Japanese essential hypertension patients with non-insulin dependent DM were treated with manidipine or delapril for 3-months, that was an open trial, in which an improved insulin sensitivity index along with glucose effectiveness was seen. Further no differences between plasma glucose, total cholesterol and triglycerides or lipoprotein cholesterol fractions along with body weight was observed.[80] A multicenter trial that was double-blinded tried to find the difference in effectiveness along with safety profile of manidipine and enalapril in patients presenting with T2DM with hypertension for 24-weeks demonstrated marked decreases in HbA1c from 6.7% to 6.2% and blood glucose levels from 152 to 143 mg/dL, only in the manidipine group (p<0.05). No significant alterations were seen regarding other metabolic parameters.[65]

Actions of combination of manidipine with ACEi on insulin sensitivity and metabolic inflammatory and prothrombic, markers were evaluated in the MARCADOR study. This study possessed a prospective randomized open, blinded end-point (PROBE) design, where 120 subjects ranging from 35-75-years having stage I-II essential hypertension along with MetS were randomized to get either amlodipine 10 mg, temisartan 80 mg, manidipine 20 mg or manidipine 10 mg with lisinopril 10 mg. Following 14-weeks of therapy in contrast to amlopdipine, manidipine 20 mg, this group had a significantly better efficacy on IR (-26.5% *vis a vis* -3.0%), LDL cholesterol (-6.8 *vis a vis* +1.7%) and other metabolic factors. While manidipine correlated with slight rise in insulin sensitivity than manidipine with lisinopril, this combination had much greater efficacy regarding improvement of other metabolic factors from amlodipine, temisartan, manidipine combination.[81] MARIMBA Study had 64 patients without DM but having MetS, along with impaired fasting glucose (>5.6 nmol/l) and hypertension, had a randomization for manidipine 20 mg or amlodipine 10 mg for 12-weeks. Although equal decrease in BP was observed with both, plasma adiponectin, (that reflects inverse correlation with the formation of IR and MetS) was enhanced (32.9%; p=0.011) and plasma TNF-α was decreased by manidipine (-37.1%; p=0.019), but no significant alteration occurred in either with amlodipine, the HOMA insulin resistance index was decreased by manidipine significantly (-21.3%; p=0.007) but not through amlodipine (-8.3%, p=0.062).

Regarding the AMANDHA study, effectiveness, with safety of addition of manidipine 20 mg or amlodipine 10 mg over and above the treatment of subjects having DM and uncontrolled hypertension with microalbuminurea, inspite of treatment using whole dosage of a renin-angiotensin–aldosterone system inhibitor for 6 months mimimum got evaluated by both therapies. Equivalent reduction of BP took place with both.[62] Post adhoc evaluation, insulinization rates and alterations in insulin dose during the study got examined. Oral antidiabetic use and insulin got adjusted during the study as per the local practice. HbA1C at baseline was 8.1±1.1% in the manidipine group 8.2±1.0% in amlodipine one. Following 2 years of therapy was 7.6±1.3% and 7.9±0.9% respectively (p=NS). 72.2% patients treated with manidipine and 73.3% treated with amlodipine were receiving insulin therapy. Of these dosage of insulin was 0.47±0.13 U/Kg and 0.44±0.16 U/Kg respectively. Following 2 years of therapy insulin dosage was 0.36±1.1 U/Kg and 0.51±1.7 U/Kg respectively (p[manidipine *vs* baseline]=0.031; p[manidipine *vs* amlodipine=0.012]). Additionally, of those not getting insulin therapy at baseline, 11.8% of patients of manidipine group and 50% of those from amlodipine one had to initiate insulin therapy during the study (RRR 76.4% absolute risk reduction 38.2%; odds ratio 7.5)

Fogari R et al compared the actions of manidipine with dalapril *vis a vis* olmesartan/hydrochlorthiazide combination treatment in old patients with DM and hypertension, and randomized 158 subjects to get 10 mg manidipine with 30 mg dalapril or 20 mg olmesartan with 12.5 mg hydrochlorthiazide for 48-weeks duration. Once the study finished, inspite of similar decrease in sitting BP, no alterations in metabolic profile was seen with manidipine with dalapril, a rise in HbA1c (±0.4 mg/dL; p<0.05), and triglycerides (+41.3 mg/dL; p<0.05), and decrease in HDL-Cholesterol (-3.4 mg/dL; p<0.05), were observed in olmesartan/hydrochlorthiazide Group.[82] Another study carried out in 88 obese hyper-

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tension subjects, manidipine with dalapril group but not olmesartan/hydrochlorthiazide group significantly reduced IR along with plasma fibrinogen levels, inspite of similar BP reducing effectiveness.[83] One more study by Kohlmann et al. In patients with DM and hypertension with microalbuminurea, showed that while BP reducing effectiveness was equivalent in both groups following 1-year of follow-up, a pattern of decrease in blood glucose levels from baseline with manidipine with dalapril group (mean change -0.2 mmol/L; p=0.064), but not with losartan/hydrochlorthiazide combination.[84]

Further there are reports regarding strong statins having the capacity to help in DM development.[85] Liberopoulos et al[86] tried comparing manidipine 20 mg with rosuvastatin 10 mg with olmesartan 20 mg with rosuvastatin 10 mg on markers of IR in subjects having dyslipidemia, hypertension and impaired fasting glucose 3 months of therapy, significant enhancement of HOMA-IR index by 14% (from 2.4 to 2.7; p=0.02 *vs* baseline) was documented for olmesartan with rosuvastatin, while no significant alteration was found with manidipine with rosuvastatin (1, 7 to 1.7, p=NS *vs* baseline, p=0.04 *vs* olmesartan with rosuvastatin group). Additionally, increased fasting insulin was seen in olmesartan with rosuvastatin group (from 10.1 to 10.9 μU/mL; p<0.05 *vs* baseline) but not with manidipine with rosuvastatin (from 7.3 to 7.59 μU/ml; p=NS *vs* baseline, p=0.02 *vs* olmesartan with rosuvastatin group). No changes in fasting plasma glucose or glycosylated haemoglobin was seen in either group. Thus this reveals that manidipine abrogates the probable statin–related enhancement of IR in comparison with olmesartan.[86]

A study particularly having a design for evaluating the action of various dihydropyridine calcium channel blockers (amlodipine 5-10 mg, felodipine 5-10 mg, lacidipine 4-6 mg and manidipine 10-20 mg), for 24-weeks on plasma norepinephrine in essential hypertension subjects, a significant elevation in plasma norepinephrine concentration were seen with amlodipine and felodipine (+34.9% and +39.4% respectively; p<0.001 *vs* placebo) but not with lacidipine (+7.1%; p=NS) and manidipine (+2.9%; p=NS).[87] Conversely, a study comparing actions of manidipine with dalapril and irbesartan–hydrochlorthiazide combinations on fibrinolytic action in hypertension subjects with T2DM, where although manidipine with dalapril combinations increased fibrinolytic action, this function was worsened with irbesartan –hydrochlorthiazide combinations.[88] Variations in SNS activation stimulated with chronic therapy with dihydropyridine calcium channel blockers along with various functions on fibrinolytic function might affect the CVS outcomes. Actually studies showed that simvastatin with manidipine interaction a positive way in heart protection from ischemia-reperfusion injury.[89]

Lastly, as variations in sympathetic excessive activation following arterial vasodilation have been demonstrated to have variations in ankle oedema rates, calcium channel blockers which activate SNS to a minimum amount might cause less chance of ankle oedema.[61] This is observed with manidipine in contrast to amlodipine.[90]

ONTARGET/TRANSCEND TRIALS

Further in the ONTARGET/TRANSCEND studies, Bohm et al identified 11,487 patients with DM or without DM19450 patients out of a total of 30,937 subjects, picked up from 133 centres from 44 countries, having a median follow-up of 56-months. These patients had a history of stroke, MI, PAD or were high-risk diabetics. Patients in ONTARGET were randomized to ramipril 10 mg, telmisartan 80 mg daily, or the combination of both. Patients in TRANSCEND were intolerant to ACE and thus randomized to telmisartan 80 mg daily or matching placebo. Evaluation of association of mean achieved initial systolic blood pressure (SBP) and diastolic blood pressure (DBP) with composite outcome of CV death, MI, stroke and hospitalization for CHF, the components of the composite, and all cause death. In patients with DM, event rates were higher across the whole spectrum of SBP, and DBP as compared to those without DM (p<0.0001 for the primary composite outcome, p<0.01 for all other events). Mean achieved in trial SBP≥160 mmHg was related to an enhanced risk for the primary outcome [DM/No DM; adjusted HR 2.31 (21.93-2.76)/1.66 (1.35-2.02)] compared with non DM with SBP 120 to <140 mmHg], with equivalent observations for all other endpoints in patients with DM, and for MI and stroke in patients without DM. Initial SBP < 120 mmHg correlated with greater risk for the combined outcomes in patients with DM [HR 1.53 (1.27-1.85)], and for CV death and all cause death in all patients. Intrial DBP ≥ 90 mmHg correlated with higher risk for the primary outcome [DM/No DM: HR 2.32(1,91-2.82)/1.61(1.35-1.93) as compared with non-DM with BP 70 to <80 mmHg], with equivalent observations for all other endpoints, but not for CHF hospitalizations in patients without DM. Initial DBP<70 mmHg correlated with >risk for the combined outcomes in patients (DM/No DM:HR1.77 (1.51-2.06)/1.30(1.16-1.46)), and also for all other endpoints except stroke. Thus concluding treatment BP levels (≥160 or ≥90 mmHg correlated with hgher risk of CVS outcomes and death. Further even low-levels (<120 or <70 mmHg correlate with higher CVS outcomes (except stroke) and death. Subjects with DM possess consistently higher risks over whole BP range, that suggests that optimal BP goals has biggest impact in this group. These results favour guidelines taking lower BP boundaries into consideration, especially in DM.[91]

DISCUSSION

T2DM with hypertension subjects demonstrate a high CVS risk.[1-3] The American Diabetes Association (ADA) guidelines give a target of 140/90 mmHg for subjects with T2DM (A is the level of recommendation) but a value of <130/80 mmHg is alright for some diabetics having higher risk of CVD, if attained without any treatment burden (level of recommendation C).[92] A lot of subjects with T2DM with hypertension don't achieve these BP targets.[29,30] Actually most of subjects with T2DM with hypertension will need a minimum of 2 drugs for reaching these BP targets.[33,93] The ADA guidelines distinguish recommendations on the basis of CVD risk. High-risk subjects with T2DM need to have a BP<130/80 mmHg while subjects having low CVD risk need to have a BP>140/90 mmHg.

A practical method is needed to decrease risk of CVS in T2DM.[2,45] Thus in these subjects preferably use of antihypertensives drugs which have shown a positive action on metabolic factors. Thus utilization of an ACEi or ARB, but not the two together is important[26,92,94] following the ACCOMPLISH Trial, further use of dihydropyridine calcium channel blockers as add on therapy is recommended on need.[37,38]

But not all dihydropyridine calcium channel blockers are equivalent as far as their effects on metabolic factors are concerned. Manidipine has a positive action on these metabolic factors, helping in reducing insulin dosage in contrast to amlodipine.[68] Additionally, manidipine has positive actions regarding oxidative stress has been documented.[94] Far less SNS activation, thus lower metanephrines, HR, PR, ankle oedema and better in DM with MetS.

The ONTARGET/TRANSCEND studies, in large number of subjects showed that with DM, Bohm et al showed that BP levels (≥160 or ≥90 mmHg correlated with higher risk of CVS outcomes. Further even low-levels (<120 or <70 mmHg correlate with higher CVS outcomes (except stroke) and death. Subjects with DM possess consistently higher risks over whole BP range, that suggests that optimal BP goals has biggest impact in this group. These results favour guidelines taking lower BP boundaries into consideration, especially in DM.

CONCLUSION

Therefore, the drug of choice in subjects presenting with T2DM with hypertension remain renin-angiotensin–aldosterone system inhibitors. If a 2nd antihypertensive is required, a dihydropyridine calcium channel blocker needs to be opted for, where manidipine is a much better choice in contrast to amlodipine. Gupta et al analyzed prescriptions in consecutive patients with T2DM at 9 sites in India, of which hypertension therapy details were available in 8056 of 8699 subjects (n=4829 men, n=3227 women), no hypertension was present in 3300 (40.9%) hypertension in 3625 (45.0%) hypertension with vascular disease in 1131(14.0%). In DM patients having no hypertension, hypertension and hypertension with vascular disease, respectively prescription in antihypertensives drugs was: renin-angiotensin–system (RAS) blockers in 19.4, 48.2 and 58.1%, beta blockers in 4.8, 31.6 and 38.8%, calcium channel blockers in 0.4, 27.4 and 14.3% and diuretics in 0.6, 36.4 and 17.1%. ACEi were prescribed is more than ARB's in hypertensive diabetics (60.7 *vs* 39.2%) along with in DM patients having vascular disease (58.6 *vs* 41.4%). In DM with hypertension (n=3625), prescription of 1, 2 or 3 antihypertensives drugs was 49.8%, 33.7% and 3, 5%, while statins was prescribed in 54.1%. Thus they demonstrated that use of ACEi or ARB's in both uncomplicated hypertensives patients with T2DM remains suboptimal. Most of the patients are on 1 drug and prescription of ≥ 3 drugs are rare with statins being prescribed only in 50% subjects.[96] This is one example of how >2 antihypertensives are not being used currently in most of the world, which needs, emphasis. Like we had earlier emphasized on the importance of use of empigliflozin in treatment of T2DM for a better CVOT,[97] similar results have been emphasized by the EMPRISE study results.[98] Huang et al in a retrospective study on the risk of new onset DM (NOD) with antihypertensive drugs found that after adjusting all parameters, risk of NOD was highest with thiazide diuretics and nondihydropyridones CCB's were at higher risk of developing NOD in Taiwan.[99] Further as we have been emphasizing on the use of plants products like monoterpenes and other plant products like PTB Inhibitors (unpublished observations), Chukwama et al reviewed 64 studies with plant species that matched there selection criteria. Members of the *Fabaceae* family were the most investigated plants, while the ω greatly varied across the plants, with only 11 plants having a ω=1. *Withania somnifera Dunal* was the only plant reported to show blood glucose lowering and diuretic effect in humans compared to daonil. Caffeic acid, chlorogenic acid, caftaric acid, cichoric acid, verbascoside, leucosceptoside, fucoxanthin and nicotinamide were the reported dual acting antidiabetic and antihypertensive compounds pointed and/or isolated in the plants. Thus suggesting that medicinal plants have different therapeutic dynamics against hypertension and DM which might get exploited to discover therapeutic preparations/agents to treat both diseases.[100] Limitations of the study is that we have mainly studied obese diabetics and hypertensives. Best option of treatment would be the 4th generation calcium channel blocker (CCB), Cilnidipine with Ace inhibitors or ARb'S.[101] Already we have started using the 4th generation CCB, Cilnidipine in our antenatal patients with Pregnancy-induced hypertension (PIH) in view of non-availability of labetolol and are carryimg out double blind trials to study them and need to further study it and start using it in diabetic hypertensives instead of amlodipine being currently used. Further with the advent of 4th generation CCB Cilnidipine with ACEi were detected to have an edge over nephroprotection, reducing microalbuminurea and reduction of symphathetic activity. Therefore, more trials are required with combining Cilnidipine with ACEi or ARB's in hypertensive diabetics with or without obesity[102,103] with double blind trials all over world with regards to use of these 2 combinations together to reduce SNS metabolic complications along with reduction of insulin dosage. Thus, right now best treatment recommended is enalpril with cilnidipine as one example or other ACEi or ARB's with cilnidipine.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Cross-Sectional Associations between Physical Activity and Internet Addiction among Undergraduate Students in Taiwan

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ABSTRACT

Purpose
Internet addiction is a major health concern among undergraduate students; however, few studies have addressed modifiable behavioral factors associated with internet addiction in the context of Taiwan. This study aimed to investigate associations between physical activity and the risk of internet addiction among undergraduate students in Taiwan.

Methods
In 2017, we recruited 320 undergraduate students from Northern Taiwan to participate in a cross-sectional questionnaire-based survey. Physical activity was measured by the Taiwanese short-form version of the International Physical Activity Questionnaire, which evaluates an individual's weekly levels of vigorous-intensity aerobic physical activity (VPA) and moderate-intensity aerobic physical activity (MPA). Internet addiction was measured by the Chen Internet Addiction Scale (CIAS).

Results
For the 320 surveyed students, the average CIAS score was 53.3, and 18.13% of participants were at risk for internet addiction (defined as CIAS score >64). The results of the multiple regression analysis indicated that a routine of at least 150 min of MPA per week was negatively associated with risk for internet addiction (β=−4.39, 95% CI=[-8.10, -0.66]). No significant associations were observed between internet addiction and 75 min of VPA or 150 min of total physical activity per week. Among the 5 dimensions of the CIAS scale, MPA was negatively associated with tolerance symptoms, time-management problems, and interpersonal and health-related problems when a routine of 150 min per week was adopted.

Conclusion
A routine of 150 min of MPA per week was associated with a lower risk for internet addiction. Intervention efforts aimed at reducing undergraduate students' problematic internet use should promote recommended levels of MPA. We also recommend longitudinal research on the effects of engaging in physical activity on the risk of internet addition.

Keywords
Physical activity; Internet addiction; Undergraduate students.

INTRODUCTION

The internet usage rate has increased rapidly worldwide, and internet use has become an integral component of leisure time. In 2005, the number of internet users was one billion around the world, and in 2019, the number of internet users reached four billion.[1] Because of technological advancements, people use the internet to enjoy leisure time, strengthen interpersonal relationships, and learn new information efficiently. However, excessive and out-of-control internet use may lead to undesirable outcomes, such as educational or health problems.[2-5]

The conceptualization and operationalization of internet addiction have been debatable in past decades.[6] Internet addiction

disorder, defined as the inability to control internet use, can lead to physical, psychological, and social difficulties.[7] Internet addiction, a type of behavioral addiction, also defined by the Diagnostic and Statistical Manual of Mental Disorders with respect to the following factors: tolerance, withdrawal, larger amounts, impaired control, time spent, neglect of activities, and continued use despite problems.[8,9] Considering the popularity of the internet, the risk of internet addiction may become a major public health concern, but the literature on the efforts on prevention of internet addiction is limited.[10] To develop interventions targeting on internet addiction prevention, the exploration of modifiable behavioral factors associated with internet addiction is necessary.

The World Health Organization (WHO) has recommended a specific level of physical activity for adults between the ages of 18 and 64-years. Activities were measured in metabolic equivalents (METs). For adults, one MET is defined as 1 kcal/kg/hour and is roughly equivalent to the energy expenditure of sitting quietly. Moderate-intensity activities burn 3-6 METs, vigorous-intensity activities burn >6 METs; walking, for example, consumes 3.5 METS.[11] Factors that may affect physical activity levels have been well-studied, and the link between screen time and physical activity has been proposed. People with excessive screen time may participate in insufficient physical activity.[12,13] However, notwithstanding studies on excess screen time, little is known regarding whether problematic internet use, particularly internet addiction, is associated with physical activity. The purpose of this study was to investigate the cross-sectional association between physical activity and risk of internet addiction among undergraduate students.

MATERIALS AND METHODS

Study Participants

We conducted a cross-sectional survey in Northern Taiwan in 2017 and recruited 320 undergraduate students. Sample size was determined by 95% confidence level and a confidence interval of 5. No incentive was provided for participants. The Institutional Review Board of National Taiwan Normal University approved the procedure and materials used in this study.

Measurements

The data used in this study were collected using a self-administrated questionnaire developed. Two valid and reliable scales were applied: the International Physical Activity Questionnaire (IPAQ)[14] and the Chen Internet Addiction Scale (CIAS).[15] Sociodemographic information, including sex, age, school type (university *versus* vocational college), and employment status, was also collected.

Physical activity was measured using the Taiwanese short-form version of the IPAQ, which evaluates an individual's weekly vigorous-intensity aerobic physical activity (VPA) level, moderate-intensity aerobic physical activity (MPA) level, and walking habits. According to the recommended levels of physical activity for adults, surveyed participants' VPA level was classified by whether the individual achieved at least 75 min of VPA throughout the week; MPA level was classified by whether the individual achieved at least 150 min of MPA and walking throughout the week; and total physical activity was classified by whether the individual achieved at least a 150-min equivalent combination of VPA, MPA, and walking.

The CIAS was used to measure the risk of internet addiction. The CIAS consists of 26 items, and it evaluates five dimensions concerning internet addiction: compulsive use of the internet, internet addiction withdrawal symptoms, internet addiction tolerance symptoms, interpersonal and health-related problems, and time-management problems. Compulsive use of the internet, internet addiction withdrawal symptoms, and internet addiction tolerance symptoms were defined as the core symptoms of internet addiction, and interpersonal and health-related problems and time-management problems were defined as problems associated with internet addiction. Each response was scored on a 4-point Likert scale. A higher score indicated a higher risk of internet addiction. Those with total scores higher than 64 were classified as being at risk for internet addition.

Statistical Analysis

Data were analyzed using descriptive statistics and multiple regression analysis in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Significance was set at a p value of 0.05 or less. The regression model was adjusted for sociodemographic variables, including sex, age, school type, and employment status.

RESULTS

For the 320 surveyed undergraduate students, the average CIAS score was 53.3, and 18.13% of participants were at risk for internet addiction (Table 1). In terms of IPAQ, 45.63% of participants reported at least 75 min of VPA per week, 79.69% reported at least 150 min of MPA per week, and 59.06% reported at least 150 min of total physical activity per week.

Multiple regression analysis results indicated that a routine of at least 150 min of MPA per week was negatively associated with the risk of internet addiction (β=−4.39, 95% CI=[-8.10, -0.66]). No significant association was observed between the risk of internet addiction and 75 min of VPA or 150 min of total physical activity per week (Table 2).

With respect to the five dimensions of internet addiction, a routine of at least 150 min of MPA per week was negatively associated with tolerance symptoms, time-management, and interpersonal and health-related problems. No significant association was observed between physical activity and withdrawal symptoms or compulsive use symptoms (Table 3).

DISCUSSION

The findings of this study indicated that a routine of at least 150 min of MPA per week was negatively associated with the risk of internet addiction in the context of Taiwan. In this study, we further analyzed the five dimensions of the CIAS and found that a routine of 150 min of MPA was negatively associated with tol-

Table 1. *Demographic Characteristics, Internet Addiction Risk, and Physical Activity Level of 320 Surveyed Undergraduate Students*

	N	%	Mean	SD
Sex				
Male	131	40.94		
Female	189	59.06		
Age			22.4	1.5
School Type				
University	298	93.13		
Vocational College	22	6.88		
Employment Status				
Not employed	142	44.38		
Full-time/ part-time job	178	55.62		
CIAS Score			53.3	13.7
Internet Addiction Risk				
No risk	262	81.88		
At risk	58	18.12		
VPA				
<75 min/week	174	54.38		
>=75 min/week	146	45.62		
MPA				
<150 min/week	65	20.31		
>=150 min/week	255	79.69		
Total PA				
<150 min/week	131	40.94		
>=150 min/week	189	59.06		

SD: Standard deviation; CIAS: the Chen Internet Addiction Scale;VPA:Vigorous physical activity; MPA: Moderate physical activity; PA: Physical activity.

Table 3. *Multiple Regression Models of Physical Activity and the Five Dimensions of Internet Addiction Measured Using the CIAS*

	F	B	95% CI	*p* value
Tolerance Symptoms				
VPA (reference: <75min/ week)	1.21	-0.32	(-0.92,0.27)	0.28
MPA (reference: 150min/ week)	1.81	-0.91	(-1.63,-0.20)	0.01
Total PA (reference: <150min/week)	1.12	-0.17	(-0.77,0.42)	0.56
Withdrawal Symptoms				
VPA (reference: <75min/ week)	1.26	-0.40	(-1.11,0.30)	0.26
MPA (reference: 150min/ week)	1.18	-0.27	(-1.37,0.33)	0.23
Total PA (reference: <150min/week)	1.28	-0.52	(-0.97,0.43)	0.43
Compulsive Use				
VPA (reference: <75 min/ week)	1.75	-0.47	(-1.20,0.27)	0.21
MPA (reference: 150 min/ week)	1.75	-0.56	(-1.45,0.33)	0.22
Total PA (reference: <150min/week)	1.71	-0.41	(-1.15,0.32)	0.27
Time Management Problems				
VPA (reference: <75 min/ week)	2.26	-0.35	(-1.08,0.37)	0.34
MPA (reference: 150 min/ week)	3.06	-1.23	(-2.10,-0.36)	0.01
Total PA (reference: <150 min/week)	2.25	-0.34	(-1.07,0.38)	0.35
Interpersonal and Health-related problem				
VPA (reference: <75 min/ week)	3.06	-0.59	(-1.50,0.31)	0.20
MPA (reference: 150 min/ week)	3.39	-1.16	(-2.25,-0.07)	0.04
Total PA (reference: <150 min/week)	3.27	-0.85	(-1.75,0.06)	0.07

Adjusted: sex, age, type of school, and employment status
CIAS: the Chen Internet Addiction Scale,VPA:Vigorous physical activity, MPA: Moderate physical activity, PA: Physical activity.

Table 2. *Multiple Regression Models of Physical Activity and CIAS Scores*

	F	B	95% CI	*p* value
VPA (reference: <75 min/week)	2.13	-2.14	(-5.22,0.95)	0.17
MPA(reference: 150 min/week)	2.54	-4.39	(-8.10,-0.66)	0.02
Total PA (reference: <150 min/week)	2.11	-2.05	(-5.13,1.05)	0.19

Adjusted: sex, age, type of school, and employment status
CIAS: the Chen Internet Addiction Scale,VPA:Vigorous physical activity, MPA: Moderate physical activity, PA: Physical activity.

erance symptoms, time-management problems, and interpersonal and health-related problems. In previous literature, physical activity is also reportedly associated with a low risk of problematic internet use among Korean adolescents.[16] Students spend a great deal of time using the internet, which might limit the amount of time that they can devote to physical activity. Data from Pakistan also indicated that the prevalence of internet addiction is higher among students who do not participate in any physical activity compared with those who do.[17]

A possible explanation for this negative association is self-control. It was previously observed that higher levels of self-control and self-management skills can reduce the risk for internet addiction. If individuals enhance their self-control and self-management skills, their risk for internet addiction may consequently be reduced.[18] A study of Korean adolescents suggested the effect of sports participation on internet addiction mediated by self-control.[19] Future study may investigate the mediation effects of life skills, such as self-control, time management, goal setting, or decision making, on the associations between physical activity levels and internet addiction.

Using two valid and reliable scales to measure the level of physical activity and internet addiction, this study indicated that a routine of 150 min of MPA per week was associated with a lower risk of internet addiction, particularly tolerance symptoms, time-management problems, and interpersonal and health-related problems. In the existing literature, little is known about the association between physical activity and internet addiction risk in the context of Taiwan. Among youths in Taiwan, the prevalence of internet addiction was noteworthy,[20] and it related to lower health-related quality of life.[21] Intervention efforts aimed at reducing undergraduate students' problematic internet use should promote student participation to ensure recommended levels of MPA. MPA is usually recommended as an appropriate form of regular exercise because it does not require specific skills or equipment and is convenient to engage in. Regular MPA can be an alternative behavior of internet use, which is an intervention strategy to reduce the risk of internet addiction.

LIMITATIONS

This study employed a self-administrated questionnaire-based survey; thus, recall bias is a possible limitation. Information on the details of internet use habits, such as the activities types that participants have done online, was not collected. The purposive sampling method also limits the representativeness of the study sample. Moreover, causality between physical activity and internet addiction could not be conclusively determined in this cross-sectional study. Future research on the longitudinal effects of physical activity on the risk of internet addiction is recommended.

CONCLUSION

A routine of 150 min of MPA per week was negatively associated with the risk of internet addiction among surveyed undergraduate students in Taiwan. Intervention efforts aimed at reducing problematic internet use should promote recommended levels of MPA in this population.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Systematic Review

The Association of Dietary Fatty Acids and Gut Microbiota Alterations in the Development of Neuropsychiatric Diseases: A Systematic Review

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ABSTRACT

Aim
Having reviewed earlier the role of probiotics in obesity and other associated metabolic disorders like non-alcoholic fatty liver disease (NAFLD), engineering probiotics for cholera and other neuronal diseases like Alzheimer's, Parkinson disease with incidence of obesity and diabetes mellitus (DM) so much on the rise, Here the aim of this systematic review is to highlight the influence of dietary patterns, like fatty acids, other lipids on role of maternal stress and the neuropsychiatric disease (NPD) formation along with influence of probiotics in reverting them.

Method
A systematic review was carried out using the PubMed, Web of Science, Medline, Embase, Cochrane reviews, and Google Scholar, Search engine with the MeSH Terms; "Impaired lipid metabolism"; "Oxidative stress"; "inflammation"; "Gut Microbiota (GM)"; "NPD"; "Schizophrenia (SCZ)"; "Autism Spectrum Disorder (ASD)"; "Bipolar disorders (BD)"; "Gamma amino butyric acid (GABA)"; "5-hydroxy tryptamine (5HT)"; "Brain derived neutrotrophicfactor (BDNF)"; "Polyunsaturated fatty acids (PUFA)"; "Saturated (SFA)"; "Depression"; "Resolvins"; "Protectins"; "Short chain fatty acids (SCFA)"; "Probiotics"; "Fecal Transplantation" from 1990 till June 2020.

Results
We found a total of 900 articles under various subheadings of GM and NPD and probiotics with NPD and SCZ, ASD. One hundred ninety-two (192) articles got selected for this comprehensive review. No meta-analysis was conducted.

Conclusion
We observed a marked correlation among dietary habits, like utilization of Western diet (WD) with marked escalation of intake of high fat, high sugar rich diet escalated n6 PUFAS over n3 PUFAS and influence on GM that is not helpful in digestion of the non-digestible fibers in form of starch along with generation of butyrate aiding in certain beneficial effects and on formation of various neurochemicals like escalation of BDNF while increased GABA, reduced 5HT formation alteration of tryptophan metabolism is seen in these WD food and we have tried to detail the role of SCFA formation, generation of resolvins and how they work in the formation of various NPD besides maternal diet during pregnancy and how it determines infants microglial priming and later determinants of early stress.

Keywords
Dietary fat; Western diet; Microbiota to brain communication (MBC); Polyunsaturated fatty acids (PUFA); Gut microbiota (GM); Schizophrenia (SCF); Autism spectrum disorder (ASD).

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INTRODUCTION

It has been realized that what our dietary habits are, in addition to what diet comprises of besides the way it is consumed has a strong influence on brain health. Over the past few years extensive work has been conducted to understand the critical significance of trillions of bacteria that are present in the gastrointestinal tract (GIT) along with dynamic interaction among the heterogenous make-up of this large microorganism community along with chances of getting various diseases like obesity, type 2 diabetes mellitus (T2DM), pain, neurodevelopmental, neurodegenerative as well as neuropsychiatric diseases.[1] An ecosystem comprised of trillions of commensals in the form of bacteria, archaea, protozoa as well as viruses whose collective microbiome is known as microbiota.[2] Further we have reviewed in various studies, it has significance that bidirectional gut-brain dialogue occurs *via* a complicated communication network that is inclusive of the sympathetic as well as parasympathetic branches of the autonomic nervous system (ANS), the hypothalamo-pituitary-adrenal axis (HPA) axis of the endocrine system, the immune system as well as the enteric nervous system (ENS).[3] Parallel to this the liberation of enteroendocrine hormones can remarkably modulate host physiology. Actually, enteroendocrine hormones cells liberate various hormones like glucagon like peptide 1 (GLP1), peptide-YY (PYY), cholecystokinin (CCK), as well as serotonin (5HT), with a crucial influence on nutrient absorption, metabolism as well as appetite,[4] as well as further manipulate anxiety–like behaviors.[5] Hence gut-brain axis has a part in integrating hormonal, immune as well as neural signals in a communication system by which the gut microbiota (GM) community as well as its metabolites as well as permeability, mucosal immune function,[6] along with influence brain neurochemistry and processing of emotional as well as rewarding behaviors.[3,7] In this complex system, bacterial metabolites like short chain fatty acids (SCFAS) (like butyrate or butyric acid (BA), acetate (AC) as well as propionate or propionic acid (PPA), immune mediators (chemokines), signals as well as bidirectional crosstalk through the vagus nerve represent the main routes that bring about microbiota to brain communication (MBC). For further corroboration of crucial part of vagus pathway, both harmful actions through lipopolysaccharide (LPS) delivery or advantage of probiotics supplementing get suppressed or blunted through inactivation of vagal communication.[6,8] Afferents from vagus nerve to brain impact the hypothalamo- pituitary adrenal (HPA) axis action along with coordinated responses to physical as well as emotional stressors, as well as liberation of hypothalamic corticotrophin releasing factor (CRF) as well as adrenocorticotropic hormone (ACTH) liberation *via* pituitary gland.[9] After having reviewed the GM in obesity as well as non-alcoholic fatty liver disease (NAFLD), metabolic disorders, proteins and GM, probiotics in obesity as well as NAFLD, engineering probiotics.[10-14]

i) We concentrated on association among microbiota as well as brain disorders.

ii) Emphasis was laid on correlation among dietary lipids, changes in microbiota-brain communication (MBC), as well as vulnerability to NPDs like schizophrenia (SCZ), depression as well as autistic spectrum disorders (ASD).

iii) Influence of selected dietary lipids, whether they had a protective or preventive potential against pathogenesis of neuropsychiatric disease (NPD). Of fatty acids (FA's) especially significance of poly-unsaturated fatty acids (PUFA), their role in chronic inflammation situation as well as function of pro resolving mediators in protecting from NPD was attempted.

iv) Western diet (WD)-global nutrition with significance of WD in inducing chronic inflammatory situations affecting intestinal as well as brain physiology was elaborated.

v) Diet composition as well as gut bacteria metabolites, along with their ability to synthesize short chain fatty acids (SCFA) as well as contribution of SCFA absence contributed to the development of psychiatric illnesses is reviewed.[15]

METHOD

A systematic review was carried out using the PubMed, Web of Science, Medline, Embase, Cochrane Reviews, Google Scholar Search engine with the MeSH Terms; "Impaired lipid metabolism"; "Oxidative stress"; "Inflammation"; "Gut Microbiota (GM)"; "NPD"; "Schizophrenia (SCZ)"; "Autistic spectrum disorders (ASD)"; "Bipolar disorders (BD)"; "Gamma amino butyric acid (GABA)"; "5-hydroxy tryptamine (5HT)"; "Brain derived neutrotrophicfactor (BDNF) polyunsaturated fattyacids (PUFA)"; "Saturatedfattyacids (SFA)"; "Depression"; "Resolvins"; "Protectins"; "Short chain fatty acids (SCFA)"; "Probiotics"; "Fecal Transplantation" from 1990 till June 2020 was conducted.

RESULTS

We found a total of 900 articles under various subheadings of GM and NPD and probiotics with NPD and SCZ, ASD. One hundred ninety-two (192) articles got selected for this comprehensive review. No meta-analysis was conducted.

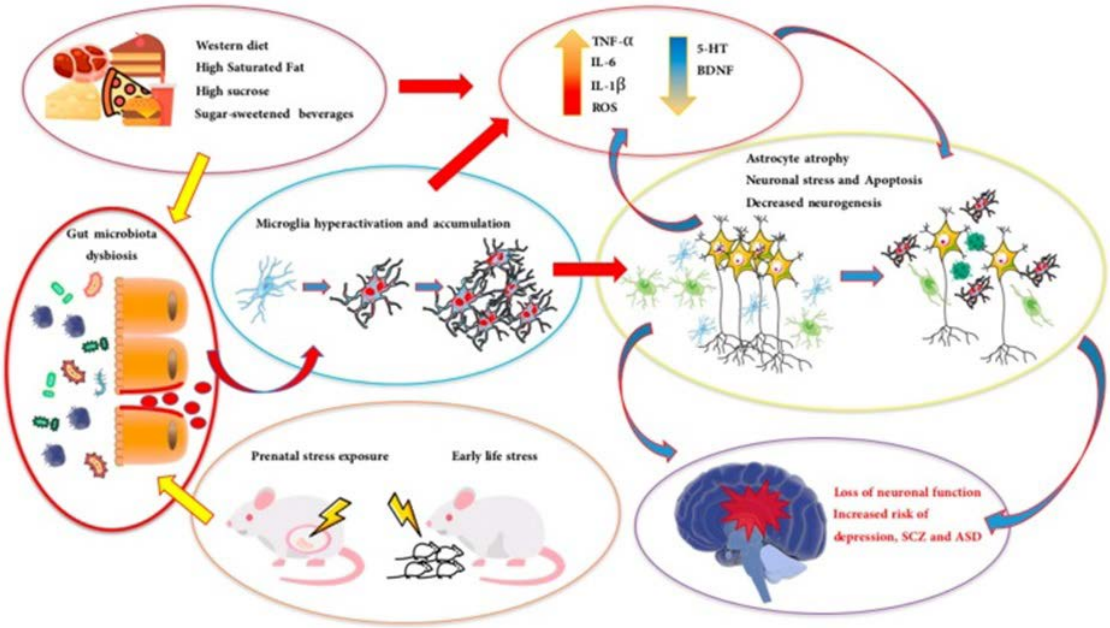
Neuropsychiatric Diseases as well as Microbiota

The changes in microbiota ecosystem might negatively influence brain physiology has been pointed with an escalated chance of psychiatric illness.[16] Further the correlation among microbiota change as well as brain disease gets suggested by the comorbidity among psychiatric disorder as well as variety of gastrointestinal (GI) diseases like irritable bowel syndrome (IBS) as well as enteropathies along with the effectiveness of probiotics (i.e psychobiotics) on stress stimulated GI symptoms, as well as anxiety along with depression.[17,18] Further unanticipated is the illustration of the pathophysiology of GI disorders or systemic inflammation can get spread among organisms *via* transfer of the GM among patients or pathological animal models to germ free mice.[19] Influence of GI diseases on mental health,[17] gets corroborated by the huge utilization of antidepressants in the population of IBS patients,[20] that convincingly support the part of emotional stress in dysbiosis, gut motility as well as epithelial integrity . It is actually well understood that prenatal, early postnatal, as well as adulthood stress have a key part in the pathogenesis of various psychiatric illnesses.[21] Microbiome can directly influence stress response, as well as germ free (GF) mice having absence of commensal GM show a hyper response towards stress, as well as exaggerated HPA activation that

has the property of overexpression of CRF gene as well as protein, escalation of plasma ACTH as well as corticosterone, as well as decreased expression of hippocampal brain derived neurotrophic factor (BDNF).[22] Significantly these actions can dramatically be ameliorated *via* colonization of juvenile (but not adult) mice with the separate strain Bifidobacterium infants or accelerated by the correlation of enteropathogenic *Escherichia Coli*.[22] Maladaptive responses in terms of reduced, anxiety-like behaviours have been detailed in GF mice along with the normalization of dysfunctional risk taking behaviours after colonizing at early formation.[1,23] Astonishingly brain formation gets dramatically influenced by the microbiome, actually morphological changes of neural dendrites have been found in the hippocampus as well as amygdala of GF mice.[23] This supports the posit that GM control brain formation in adult mature neurons too, besides in adult hippocampal neurogenesis has been detailed to be greater in GF as compared to conventional mice irrespective of postweaning microbial colonization.[24]

If removal of commensal GM escalates, the chances of maladaptive behaviours that can get fully reversed only within maturational time, the potent effect of GM on neuron plasticity as well as circuitry wiring at the time of neurodevelopment might escalate the tendency towards stress –stimulated psychiatric disorders. Anyway during formation[25] as well as adulthood, probiotics administration might abrogate social stress stimulated cognitive, behavioural (anxiety, depressions) as well as immune changes.[18,26] For this a significant study is the one where stress stimulated hyperthermia, enhancement of corticosterone amounts, anxiety as well as depressions like behaviours, got decreased following chronic therapy with *Lactobacillus rhamnosus* (JB1) probiotic.[6,23] The anti-depressant as well as anxiolytic actions of *L. rhamnosus* (JB1) therapy got mediated *via* selective escalation of GABA (B) receptors mRNA expression in the cingulate cortex as well as reduction of GABA (B) expression in hippocampus as well as amygdala as well as enhancement of GABA (A) expression in hippocampus.[6] All these alterations caused by *L. rhamnosus* (JB1) therapy in GABA brain expression got repressed following vagotomy in mice along with notable decrease in the anti-depressant as well as anxiolytic actions.[6] Hence brain neurochemical alterations implicating the GABAergic system get illustrated following probiotics administration in various animal models, as well as significance of vagus nerve integrity for keeping MBC intact as well as probiotic-correlated neurochemicals action. Actually the bidirectional GM-brain crosstalk involves neuroendocrine as well as neuroimmune signalling modes,[27] as crucial routes of communication *via* HPA axis along with vagus nerve. Regarding association of the utilization of probiotics as anti-depressant therapy, there is proof that rats undergoing chronic unpredictable mild stress for stimulating depression like behaviours had an escalated amount of Firmicutes which had positive association with colonic 5HT metabolism as well as negative one with 5HT in the

Figure 1. *The Figure Depicts the Main Impact of Different Sources of Environmental Burden on the Derangement of Gut Microbiota Ecosystem, and a Selection of Potential Mechanisms Underlying Dysbiosis-Induced Liability to Neuropsychiatric Diseases (NPDs).*



Here (left side), are depicted two recognized key pathogenetic factors such as: 1-(upper figure) the worldwide consumption of western diet characterized for instance by high saturated fat and high-sucrose foods, corn-derived fructose and carbonated beverages; 2-(lower side) multiple prenatal stress, maternal immune activation and early-life stressors. Chronic exposure to either one or both sources of environmental burden can determine systemic and brain inflammation and alteration of brain homeostasis via intestinal microbiota dysbiosis and severe immune changes such as shifting towards a persistent activation of the microglial phenotype, production of inflammatory cytokines, ROS and decrease of BDNF and 5-HT synthesis. In turn, the combination of neuronal, microglial and astrocyte damage (e.g., atrophy and reduced neurogenesis), altered synaptic and neural communication and brain inflammation contribute to the risk of depression, SCZ and ASD.[34]

prefrontal cortex (PFC), both changes of 5HT metabolism got reversed *via* treatment with *L.rhamnosus* and *Bifidobacterium longum*.[28] Role of GM in depressions is the changes of GM diversity, that is seen in depressed patients, along with the probability of using fecal transplantation for transferring the microbial "signature" of microbiota depleted animals and stimulate a depression like phenotype.[29] Further the depression like phenotype seen in GF mice can get accelerated *via* the transplantation, of depressed microbiota from patients with major depressive disorder in microbiota depleted mice.[30] From this angle minocycline-stimulated changes in microbiota composition can ameliorate the depression like behaviours exaggerated in mice *via* the exposure to chronic restraint stress.[31] Significantly, this study illustrated that chronic stress decreased Bifidobacterium species which inhibits the inflammation correlated with nuclear factor kappa B (NFɤB) pathway whereas at same time enhanced the Lactobacillus species that are implicated in inflassome activation through IL-1β liberation.[31] A 16S rRNA gene evaluation along with a wide metagenomic sequencing study recently conducted on a large cohort of depressed patients has associated various microbial taxa (i.e enterotypes) with quality of life (QOL) of participants as well as incidence of depression.[32] Like results demonstrated that decreased microbial density of Bacteroides correlates with <chances of depression as well as decreased indicators of QOL.[32] Knowing that gamma amino butyric acid (GABA) as well as dopamine (DA) are neuroactive products of microbial metabolism,[18] this study further found the DA metabolite 3, 4-dihydroxy phenyl acetic acid (DOPAC) as "gut-brain module" positively associated with mental QOL, whereas a tendency towards the correlation among escalated GABA synthesis as well as depression was also observed (Figure 1).[32]

DIETARY LIPIDS AS WELL AS GUT MICROBIAL COMMUNITY MANIPULATION

Impaired Microbial Ecosystem Neuroinflammaton, as well as Chances of NPD's

Influence of impaired MBC in the etiopathogenesis of NPD's can be evaluated in the form of systemic as well as brain inflammation along with the risk for the defense of the homeostasis of the brain. In this framework, it is of marked significance that the function of surveillance conducted by microglial cells *via* very dynamic as well as plastic morphological alterations. The microglial phenotype might switch (from "surveying" to "activated") as per the changes of neural activity, neuronal-microglial signals as well as synaptic communication (Figure 1).[34,35] Microglial cells representing the main resident as well as immunocompetent cells of the brain get activated by tissue damage, infection as well as in the course of neuropsychiatric as well as neurodegenerative diseases.[36]

Significantly, a recent proof that maternal microbiota can influence the development as well as function of microglial offspring, that finally, is based on the integrity of the maternal gut-brain interaction.[35] Various risk factors in Autism spectrum disorders (ASD) as well as schizophrenia (SCZ) pathogenesis, like generalized maternal immune activation as well as early–life stress, can stimulate besides neuroinflammation aberrant microglial activation too.[36-38] Further alteration of host immunity also occurs besides stability of resident bacterial community.[39] Proof for neuroinflammation-correlated microglial activation in SCZ as well as ASD patients has also been corroborated by positron emission tomography (PET) studies, where an enhanced expression of the translocator protein (TSPO) (a marker of microglial activation) occurred.[40] Thus, unhealthy dietary patterns can get classified as the intake of saturated fats, wich a direct connection to low-grade systemic inflammation, obesity as well as proinflammatory immune response (Figure 1).[41] Further recent proof is that microglial activated neuroinflammatory signalling has a causal association among excessive intake of high fat diet (HFD) along with hypothalamic gliosis, hence acting as a crucial player in HFD induced brain inflammation as well as deranged energy homeostasis.[42-44] In case unhealthy dietary patterns can powerfully decide the changes of host microbial community as well as dysbiosis produces microbial hyperactivity (Figure 1),[34] then the input of selected dietary lipids might markedly aid in regulating microglial activation, brain inflammation as well as finally decreasing the chances of NPD's (Table 1).

Dietary Lipids-Fatty Acids, Changes in Microbiata Diversity, as well as NPD's

Normally fatty acids (FA's) might be classified as per the number of double bonds in the side chain, from saturated fatty acids (SFA's) that lack the double bond, to mono-unsaturated fatty acids (MUFA), with a single-double bond along with poly-unsaturated fatty acids (PUFA), displaying 2 or greater double bonds in the carbon chain.[45,46] As FA's can further get classified as per the carbon chain length along with the position of the first double bond on the methyl terminal, then the full family of PUFAs can further get categorized by including the omega-3 PUFAs (n-3 PUFAs) as well as the omega 6 PUFAs (n-6 PUFAs) series. Both n-3 PUFAs as well as n-6 PUFAs are essential nutrients in view of absence of particular enzymes (i.e desaturases) they can't get manufactured de novo in mammals.[47] Due to this intake through dietary sources of the two 18 carbon (18C) essential fatty acids, linoleic acid (18:2n-6, LA) along with α linolenic acid (18:3n-3, ALA) is required to form the biologically active n-6 PUFAs as well as n-3 PUFAs, respectively. As per the chain length ,the best known n-3 PUFAs form the shorter chain precursor to the n-3 series ALA, the stearidonic acid (SDA, 18:4), the long chain (≥C20) eicosapentaenoic acid (EPA, 20:5) along with docosahexaenoic acid (DHA, 22:6). Besides the family of n-6 PUFAs include the shorter chain precursor to the n-6 series LA, the arachidonic acid (ARA, 20:4), the gamma-linolenic acid (GLA, 18:3) as well as the dihomo-γ-linolenic acid (DGLA, 20:3).[48]

Lot of proof has emphasized on the pro as well as anti inflammatory potential given through the 2 series n-6 as well as n-3 PUFAs, respectively. Knowing the harmful influence of WD on microbial ecosystem, the escalated intake of n-6 PUFAs enriched vegetable oils (like soybean, corn sunflower as well as margarines) along with red meat in the form of major sources of LA along with ARA, is the biggest factor causing the huge enhancement of n-6: n-3 ratio.[49] Significantly the pro-inflammatory chronic response

Table 1. *GM, Microglial Activation, Neuro inflammation and NPD's/Brain Alterations*

Author/s	Ref. No	GM	Neuroinflammation	Microglial Activation	Dietary Lipids	NPD/NDD	Misc.
Thion et al	35	+nt-Basic idea of study see alteration of GM dsignatures in both adult and fetuses in male 7 female	Inc female both in fetus and adiult showed > Infl signatures at 198,5 weeks adulthood and Ear;ier GM defined own signatures but near delivery maternasl GM Influenced thewir dev	Activation in womb	unhealthy	Dec chance of NPDs Decided right in womb and microglial activation Basic motive Of study More in female both in early and adult life	Proper dietary lipid given
Heneka MT	36	Only shown NDD assoc with microglia changes	Occurs in inf ,TD	By tissue damage, infection and in NPD,NDD			
Bilbo	37	Change basic idea of study to see how brain dev early life affected by environmental factors change like virus inf	Stimulated by aberrant MiA, Early life stress	Aberrant Influence brain dev esp microglia that liberate cytokines &infl factors =>proneness to NPD like ASD			
Bergdolt et al	38	Change again basic idea is how MIA influences NPD	Aberrant MA model	Abberant Microglial dev with possible epigenetic changes predispose To ASD and SCZ dev in late life			
Dinan et al	39	Changed gut has 1013 To 1014 org 10 times >cells and 150 times >genes act host genome Even *E.Coli* enters	Aberrant MA Further stress can cause inc gut permeability Lot of GM changes seen in IBS and ASD hence	Abberant Can influence HPA axis dev GF mice raised show inc stress Monocolonisation with Bifidobacterium normalizes		ASD Imp to nstudy GM Alteration In dev of IBS and Depression	
Suzuki et al	40	NC only idea of study was to see influence of Abn microglial activation on ASD dev	Augmented MA	PET Study -AUGMENTED But not altered MA in ASD Compared to controls		SCZ and ASD	PET—incr TSPO-MA-marker
Valdearcos et al	42	Changed	Present	Abnormal	HFD	Hypothalamic gliosis	Obesity

promoted *via* n-6 PUFAs is correlated to ARA-produced signalling pathway, synthesizing bioactive lipids known as eicosanoids as well as isoprostanes,[50] that get influenced in atherogenic processes, aberrant cell proliferation (like cancer), obesity, as well as irritable bowel disease (IBD).[51] The eicosanoids family are prostaglandins (PGs), prostacyclins, thromboxanes (TXs), lipoxins (LXs) as well as leukotrienes (LTs), having various parts in cytokine production along with amplifying or decreasing inflammation.[52] In contrast, n-3 PUFAs regulate inflammation by the precursor ALA mainly and then through EPA along with DHA synthesis. Actually EPA as well as DHA act as competitive substrates for n-6 PUFAs metabolism along with ALA-synthesized pro-inflammatory eicosanoids. Noticeably, a recent metabolomic study on a cohort of SCZ patients illustrated aberrantly enhanced serum amounts of SFA, MUFA as well as n-6 PUFSs as a probable sequence of greater than normal desaturation from SFAs to MUFAs and hence insufficient brain energy supply.[53]

Presently attention has been laid on the mode of inflammation resolution with n-3 PUFAs obtained lipids called "specialized pro-resolving mediators" (SPM's) which consists of various members of significant molecules like lipoxins, resolvins, protectins as well as maresins.[54] Deficiency of n-3 PUFAs have been constantly documented in SCZ patients, bipolar disorders as well as depression as well as no proof that EPA along with DHA supplementation might be advantageous in a subgroup of ASD patients.[55,56] In a longitudinal 7-years study recently, the escalation of n-6:n-3 ratio at baseline as found in a cohort of young persons with "ultra high-risk" for depression was observed to be true as well as correct anticipator of chances of forming later mood disorders.[57]

Collecting studies have evaluated the association among diet supplementation with n-3 PUFAs as well as NPDs, the influence on microbiota, symptoms of severity of patients with major depressive disorders, SCZ or ASD patients is still not well understood. By utilizing transgenic mice that have the capacity to oversynthesize n-6 PUFAs as well as enhance the n-6:n-3 ratio it has been feasible to show the formation of various pathogenic cascades that involve, metabolic endotoxaemia, fatty liver as well as cancers, besides other metabolic syndrome components.[58] Further besides exhibiting chronic inflammation (like serum LPS, intestinal permeability as well as tumor necrosis factor alpha (TNFα), interleukin 1 beta (IL-1β) as well as IL-6 overexpression) but also the

evaluation of faecal samples showed higher amounts of *Enterobacteriaceae* bacteria, with enhanced proteobacteria with decreased bacteroides as well as a *Actinobacteria phylum* (Figure 2).[57] Many, markers of gut dysbiosis along with intestinal permeability in faecal samples like greater amounts of 1-methyl nicotinamide, cysteine, histidine and spermidine agree with the probable causal association among enhanced n-6 PUFAs tissue content, abnormal alteration in gut microbiota (GM) as well as disease formation.[57] Same outcomes were documented in mice fed with high n-6 PUFAs diet.[58] In the same study it was found that the liberation of intestinal alkaline phosphatase (IAP) the major mode by which the transgenic elevation of n-3 PUFAs tissue amount can give an anti inflammatory potential, stimulate the growth of bifidobacterium, decreased LPS amount, gut permeability as well as metabolic endotoxaemia.[58]

Conversely, indirect positive actions of n-3 PUFAs dietary supplementation on the chances of forming chronic depressive symptoms have been recently detailed.[59] A randomized, double-blind as well as stratified study of the effect of family violence on child behaviour documented that n-3 PUFAs nutritional intervention in children decreased the amount of psychological aggression in adult caregivers.[59] n-3 PUFAs enriched diet exposure during pregnancy can develop a particular maternal n-3 PUFAs environment which in turn can "prime" offspring microbial composition in early life and give protection at adulthood. Actually, endogenous synthesis of n-3 PUFAs in the pregnancy time has been demonstrated to shape offspring GM as well as develop progeny against HFD-stimulated metabolic changes.[60] Though little number of studies have evaluated the correlation among n-3 PUFAs supplementation, manipulation of MBC as well as early-life stress, there is proof that longtime EPA as well as DHA supplementation can restore the GM composition in maternally separated rats.[61] Based on this, significant implication for n-3 PUFAs supplementation are there for avoidance of stress induced chances of mood disorders. As per a meta-analysis of the biological status of n-3 PUFAs in mood disorders, plasma as well as brain EPA as well as DHA amounts were found to be decreased in depression patients.[62] Significantly, inspite of inverse correlation among dietary fish intake as well as incidence of depression, as well as the positive correlation among eicosanoids synthesis, depression as well as SCZ,[63] the causative assocciation among n-3 PUFAs supplementation, Firmicutes: Bacteroides ratio as well as antidepressants action is still not clear. Like in case of depression EPA as well as DHA amounts are observed to be reduced in ASD children.[64] Further, in a placebo controlled study, plasma BDNF amounts were escalated by EPA as well as DHA diet supplementation in 1st episode psychotic patients were observed to have inverse correlation with depressive symptoms.[65] n-3 PUFAs deprived diet feeding to rats demonstrated decreased amounts of brain derived neutrotrophic factor (BDNF) expression within prefrontal cortex (PFC), an area considered to be of key significance in the pathophysiology of depression, SCZ as well as ASD.[66]

The probable mode of association among n-3 PUFAs reservoir deficiency as well as chances of NPDs might be further found in the neuroinflammatory pathways as well as neuroimmune changes correlated with depression or SCZ pathogenesis. Interestingly, a strong anti-inflammatory as well as protection action through macrophage stimulation as well as inhibition of NLRP3 inflammasome activation as well as IL-1β liberation was shown in mice fed with n-3 PUFAs enriched diet.[67] Being key parts of the innate immune response there is the activation of toll-like receptors (TLRs), that represent a family of transmembrane proteins, mostly expressed, besides on the immune cells (like macrophages) but further on cells of the intestinal epithelium (like enterocytes) where receptors get associated with avoidance of systemic low grade inflammation as well as GM colonization, like through sensing of polysaccharide A on *Bacteroides fragilis*.[68] TLRs recall the pathogen-associated molecular patterns (PAMPs) for avoidance of progression of inflammation as well as gut microbiota (GM) colonization. Regulation of immunological responses, TLRs can inhibit the activation of proinflammatory cytokines or NFκB-modulated inflammatory programme as well as preservation of intestinal homeostasis by decreasing the entry of bacterial products to cytosolic inflammasome.[69] TLRs as emphasized[70] represent necessary parts of gut immune system having the ability to control intestinal homeostasis, hence having a crucial part for resilience or susceptibility to particular situations where GM dysbiosis is common like IBD. In the same study, it was also shown that impairment of TLRs action correlates with metabolic derangement (like DM) besides with various brain pathologies like neuroinflammation that are typical of neurodegenerative diseases.[70]

LPS-forming gram–negative bacteria activate the TLR4 subtype,[70] stimulating the formation of various proinflammatory markers (like TNFα, IL-1β as well as IL-6) along with a cascade of pathogenetic inflammatory processes. From this angle, the disturbance of microbial community, as documented in SCZ patients regarding astroglial as well as microglial activation, impairment of neurogenesis as well as alterations in glutamate transmissions as well as NMDA receptor subunits.[71] Hence dietary alterations along with modulation of GM diversity might interfere with sensitivity of TLRs activation as well as form a state of lot of neuroimmune changes, enhancing the chances of neuro developmental disorders like SCZ as well as ASD. Intake of dietary fats can either escalate or ameliorate LPS amounts as well as TLR4-correlated inflammatory signalling, based on the kind of dietary fats. Actually SFAs like lauric along with palmitic acid can activate TLRs-modulated inflammatory program.[72] That a significant crosstalk does take place among the common intake of a carbohydrate-based/PUFA-enriched diet has been demonstrated to be correlated with < fasting LPS plasma amounts as well as chance of endotoxaemia.[73] The influence of LPS plasma amounts gets more clear by knowing these outcomes in the presence of earlier study, where intake of Mediterranean–like diet (like MUFA enriched) reduces the post-prandial (PP) proinflammatory response > than intake of PUFA-enriched diet as well as much > SFA-based diet.[74] Actually mixture of n-3 PUFAs/n-6 PUFAs composition might exaggerate the proinflammatory potential just above the amount of MUFA based diet, but in anyway < that given by SFA high-diet. Various evaluations have played the significance of reciprocal controlling role caused by SFAs as well as n-3 PUFAs on the activation of TLR4 as well as TLR2 subtype.[75] Besides SFAs activation, whereas n-3 PUFAs as well as especially DHA, deactivate TLR4 as well as TLR2 correlated inflammatory processes, SFA's can stimulate dimerization of TLR4 as well as TLR2 followed by translocation

of these receptors into lipid raft of the plasma membrane hence promoting the down stream signalling that is conversely inhibited *via* DHA.[72]

Without any doubt the close connection, that involves dietary fats, endotoxaemia, changes in microbiome as well as NPDs makes it complicated to get the insight of the chain processes. Still the unhealthy influence caused *via* HFD diet on proteins expression/distribution of the enterocyte tight junctions[75,76] corroborates the point that consumption of certain diet fats is the primary stimulus causing intestinal permeability as well as > susceptibility to NPDs. A significant factor correlating diet fats to intestinal barrier function as well as intestinal permeability is the susceptibility of diet lipids to escalate bile acid liberation as well as associated bile acid modulated signalling, toxicity as well as changes of enterocyte tight junction proteins.[77] The deleterious actions of SFAs on the integrity of intestinal barrier overtake that caused by the intake n-6 PUFAs-enriched HFD. Actually, animals given SFAs enriched high fat diet (HFD) show reduced barrier integrity as well as infiltration of inflammatory immune cells (like neutrophils), that are not found in n-6 PUFAs-enriched HFD or n-3 PUFAs-enriched HFD.[78] As per this diet n-3 PUFAs have been demonstrated to ameliorate experimental colitis,[79] as well as EPA given protection against inflammation-stimulated dysfunction of permeability of intestinal epithelial barrier ("leaky gut").[80]

Pro Resolving Lipid Mediators, Intestinal Inflammation and NPD's

Both pro or anti-inflammatory bioactive lipid metabolites are synthesized through the enzymatic oxidation brought about *via* cyclooxygenases (COXs), lipoxygeneses (LOXs) and cytochrome P450 (CYP450) monooxygenases. Especially from the AA the COX pathway yields PG's as well as TX's, whereas the LOX as well as LOX produces LTs as well as LXs.[81] Conversely, diet n-3 PUFAs can form enough EPA along with DHA plasma as well as brain amounts ,that are LOX as well as CYP substrates, that get steadily correlated with a strong anti-inflammatory action opposing both the expression of cytokines like TNFα, IL-1β as well inflammatory stimuli like LPS.[82]

Considering this n-3 PUFAs represent bioactive lipid modulators to facilitate the inflammation resolving through the generation of EPA as well as DHA-produced "specialized pro-resolving members" (SPMs).[54] Such EPA as well as DHA produced lipid metabolites represent anti inflammatory as well as represent the pro-resolving members' of the oxylipin family, that are resolvins (RVs), protectins (PDs) as well as maresins (MaR).[83] These resolving series are the main EPA as well as DHA produced SPMs as well as especially, resolvinE (RvE) as well as resolvinD (RvD) series once produced *via* EPA as well as DHA respectively.[84] Inspite of absence of a direct proof that RvE as well as RvD have an influence on GM, lot of evidence is there that the n-3 PUFAs confer antimicrobial effect as well as that situations where low grade chronic inflammation as well as epithelial damage (like IBD, ulcerative colitis as well as CD) get totally or partially resolved *via* resolvins-modulated amelioration of intestinal inflammation.[85] Further the DHA produced RvD1 as well as RvD2 work *via* the binding to selected G-protein coupled receptors (GPCR's), like GPR32 (DRV1) as well as GPR18 (DRV2), respectively, whereas EPA generated RvE *via* capacity to binding to Chemokine–like receptor 1, Chem R23 (ERV1).[86] Significantly exogenous delivery of high amount of RvD1 besides aiding in transepithelial resistance in SFA-enriched HFD fed mice,[78] hence relieving gut inflammation, besides removing dihydrogen sulphide (H2S) yielding bacteria as well as especially SFA-correlated escalated *Desulfovibrio* species. Regarding NPDs 2 studies gave proof of antidepressant action *via* intracerebroventricular (ICV) infusion of RvD1 as well as RvD2,[87] or EPA generated RvE 3,[88] in a mouse model of LPS-stimulated antidepressant-like behaviour. In concordance, antidepressant -like action was also detailed after ICV infusion of RvE1/RvE2 in PFC or hippocampus, probably through Chem R23 binding.[89] Thus role of n-3 PUFAs on intake or nutritional administration, EPA as well as DHA produced RVs, PDs as well as MaR provide an integrated effect having lots of immunomodulatory actions changing GM population, intestinal epithelial integrity, removal of intestinal inflammation as well as resident immune cells responding. Inspite of lot of proof supporting that diet n-3 PUFAs intake can either avoid or abrogate both NPD as well as gut dysbiosis part of EPA as well as DHA produced RVs, PDs as well as MaR in the form of microbiome as well as immune system manipulation is not clear. Actually good research has detailed the composite depressive phenotype, the escalated Firmicutes to Bacteroides ratio as well as the LPS responsiveness stimulated *via* n-3 PUFAs deficit nutritionally in case of gestational female as well as male offsprings,[90] or the avoidance actions stimulated by diet n-3 PUFAs acting on depressive–like behaviours as well as alterations of GM composition stimulated *via* social imbalance at the time of brain formation.[91] However, getting insight in the association among dietary lipids, changes in microbial ecosystem as well as chances of NPDs formation would require evaluation of RVs, PDs as well as MaR correlated signalling watching the part of the inflammation program that are the inhibition of proinflammatory modulators, the avoidance of neutrophil recruitment/infiltration, monocyte stimulation, control of polymorphonuclear neutrophils (PMN) apoptosis, clearaing of bacilli, macrophage phagocytosis getting induced as well as facilitate the chemokine scavenging.[54,83]

HT-Dopamine as well as NPDs n-3 PUFAs

Knowledge has accumulated that n-3 PUFAs-generated RVs, PDs as well as MaR have an influence in neuroprotection, whereas n-6 PUFAs-produced eicosanoids (like PG's, prostacyclins, TXs, LxS as well as LTs) have significance in the pathogenesis of NPDs like SCZ.[92] The presence of aberrations of Phospholipid turnover in SCZ is of significance. Initially, it appears that COX2 inhibitor celecoxib confers advantageous actions in SCZ patients,[93] as well as that eicosanoids might elevate DAergic neurotransmission as well as have influence besides on SCZ, as well as in refractory depression along with ASD.[94,95] In this aspect, the common consumption of n-6 PUFAs- as well as the very large amounts of ARA present in WD has the capacity to aberrantly escalate the amounts of PG', TXs, LxS as well as upregulate systemic as well as brain expression of proinflammatory enzymesa (like phospholipase A2, COX2 as well as genes (like TNF-α, IL-1β). WD stimulated subnormal n-6: n-3 ratio enhance dysbiosis of GM stimulating impairment in

the capacity of immune system to act against inflammation as well as sustain intestinal homeostasis. The inverse association among reduced peripheral as well as brain DHA amounts as well as severity of SCZ symptomatology,[96] corroborates the probability of diet n-3 PUFAs in mode of SCZ neuropathology.[97] Once there is preclinical n-3 PUFAs deficit of brain DHA amounts, it was demonstrated that it changes DA function that can be similar to that illustrated in SCZ patients.[98] In a similar way, in a preclinical form of amphetamine-stimulated SCZ like behaviour, diet n-3 PUFAs administration decreased behaviour deficiencies, cytokine release as well as elevated the action of combined antipsychotic as well as celecoxib drug therapy.[99] As brain deficit of DHA amounts might change the expression of DA receptors in ventral striatum as well as aid in hypofunctioning of, mesolimbic DA system as well as anhedonia as seen in depression,[15,100,101] the prenatal or early prenatal deficiency of n-3 PUFAs in the brain might be a key factor in pathogenesis of depression. Neurotransmitters significant for NPDs like dopamine (DA) as well as serotonin have a part in seeing to it that microbial community is preserved that is necessary for the bidirectional MBC[33] as well as both DA as well as monoamines are believed to be critical actors in the pathogenesis of SCZ as well as depression.[102] Significantly, there is proof that various kinds of dietary fatty acids might have separate actions on serotonin neurotransmission.[103] Actually 5HT2A as well as 5HT2C receptor binding was decreased in the mamillary nucleus (in the interface of the hypothalamic area) of rats with the use of a SCFAs-rich diet, whereas the intake of a n-6 PUFAs- rich diet decreased 5HT2A as well as receptor binding in the mamillary nucleus, 5HT2C receptor binding in the prefrontal cortex (PFC) as well as 5HT2 transporters (5HTT).[103] This study further emphasized on the significant belief that the main actions of brain serotonin function (receptor binding as well as transporters got stimulated *via* the intake of n-6 PUFAs-rich diet with significant influence on NPDs. Regarding DA, it further gets supported *via* the large amounts of tyrosine hydroxylase observed in small intestine.[104] Further more, antibiotics-stimulated GM removal reduces intestinal generation in mice,[105] as well as GF mice displayed unequal brain mRNA expression of DA D1 receptor (D1R), getting in the hippocampus as well as decreased in dorsal as well as ventral striatum level.[1] Thus DA metabolism gets dramatically altered *via* the changes of GM community. An imbalance among DA as well as its metabolites like homovanillic acid (HVA) as well as DOPAC have been detailed in GF rats as well as mice along with decrease in DA as well as serotonin turnover.[106,107] Significantly a reduction of HVA/DA ratio pointing to a decreased DA turnover was seen in GF rats,[107] along with cerebrospinal fluid (CSF) of patients with major depressive episode.[108] Further antibiotics-stimulated dysbiosis enhance amounts of l3,4–dihydroxy phenylalanine (L-DOPA) in PFC as well as hippocampus with both L-DOPA as well as HVA in the amygdale,[109] giving extra observation that brain DA amount, turnover as well as metabolism are associated with the changes of GM composition. The clinical utilization of atypical antipsychotic (AAP) amounts bring about remission but further change fecal GM composition in SCZ patients,[110] hence showing that AAP's therapy correlates with particular alterations in intestinal bacilli population that might reason out the various clinical effectiveness along with the severe AAP's correlation with impaired adverse actions.[111] Metabolic impairment in offspring as well as susceptibility for metabolic diseases (obesity, T2D) gets modelled at the pregnancy time with a crucial input of the close crosstalk among n-3 PUFAs as well as dietary lipids as well as GM environment. While maternal n-3 PUFAs scenario including pregnancy as well as lactation time, can markedly refashion the offspring GM in mice and give long-term protection to the progeny, the decrease of dietary n-3 PUFAs can remove the amount of species needed for gut homeostasis like Akkermansia muciniphilia.[60] Hence, in a mouse model of pregnancy depriving of dietary lipids demonstrated harmful influence on the GM synthesis of SCFAs.[112,113] Though deficiency of SCFAs correlate mainly with chances of IBD as well as metabolic diseases,[114] there is escalating proof that microbial, metabolism-produced SCFAs are critical actors in NPD pathogenesis. Knowing the harmful influence of n-3 PUFAs dietary deficiency on striato nigral as well as mesocorticolimbic DAergic neurons as well as BDNF expression,[115] along with the key part of DA neurotransmission in the NPD pathogenesis,[102] especially focus has to be kept on the future on dietary lipids correlated modes influencing the gut synthesis of catecholamines as well as manipulation of ENS (Table 2).

Gut Microbiota (GM) Community as well as SCFAs-NPD's Influence

In reference to particular dietary nutrients as influencing the changes in GM community as well as chances of NPD's, one has to pay attention on a special class of lipids generated from microbial metabolism as well as comprising of SCFAs. Nutrients handling *via* GM metabolism forms a complicated signalling system mainly made up of SCFAs, L-tryptophan (Trp) as well as metabolites along with neuroactive agents.[33,116] Trp metabolism as well as neuroactive agents are of critical signals to get insight of the association among MBC as well as chance of NPD's. GM generate a neurochemical signal intrinsically like DA, γ amino butyric acid (GABA), 5HT, acetyl choline (Ach), histamine, melatonin as well as noradrenaline,[27,117] that are critical elements for getting insight into the mode of MBC influencing the impaired behaviours like depression, anxiety as well as ASD. As precursors of peripheral as well as brain generated serotonin, the amino acid (Trp) gets converted *via* tryptophan hydroxylase (TPH) enzyme to 5HTP to 5HT by the aromatic L-amino acid decarboxylase[118] Thus Trp metabolism is needed for central serotonin generation as well as serotonin neurotransmission in both CNS, as well as in the ENS of the wall of the gut.[119] Hence as a result dietary induced alterations of microbial metabolism might possess an etiological influence in the NPD pathogenesis *via* changes in SCFAs, Trp metabolism as well as neuroactive agents. In this main concentration is on the association among unhealthy diet, impairment of SCFAs generation of as well as probable mode of depression, ASD as well as SCZ.

Microbial Community Impairment with- WD

Best study showing the robust influence of dietary habits on GM composition,[119] associates with the impact various diets generate on host physiology. The marked influence of dietary habits on microbial community is possibly associated to the effects of various diets generating in host physiology. With the worldwide adaptation of WD, maximum population of developed as well as developing

countries has shifted their diet lifestyles to exaggerated intake of high fat, high sucrose, as well as ultraprocessed food items.Without any doubt WD is responsible for the etiopathogenesis of obesity, colorectal cancer as well as chronic inflammatory situations influencing the intestines like in Crohn's disease (CD), as well as Ulcerative colitis that is part of the IBDs.[120] Highly rich in saturated fats, refined grains, corn generated fructose, proteins *via* the highly processed red meats, salt, alcohol, sweetened as well as carbonated beverages,[121] as well as its intake correlates with dysbiosis as well as impaired microbial community (Figure 1).[122] Thus WD intake alters the symbiotic association with dysbiosis as well as altered microbial ecosystem along with gut mucosa influencing host metabolism has been seen to be implicated in the intake of redmeat as well as coronary heart disease through dietary phosphatidyl choline along with synthesis of the proatherosclerotic metabolite trimethyl amine-N-oxide.[123] With lots of proof against WD as well as dysbiosis, WD is also the cause of escalated intestinal permeability as well as endotoxaemia, as proved in CD.[124] Commensals in the GIT that belong to Fermicutes phylum having proven immunomodulatory as well as anti-inflammatory actions, *Faecali bacterium prasnitzii* (*F.prausnitzi*) get decreased in patients with CD, whereas its supplementation as a probiotic is thought to be a treatment method for CD.[125] Biggest problem related to WD intake is the reduction in both microbial community thought to be protective bacteria with the expansion of pro-inflammatory as well as invasive Proteobacteria (like *E.Coli*) with dramatical decrease in SCFAs.[126] The escalation of pathogens as well as mucin breaking bacteria like the Mollicutes class of the Firmutes phyla, that includes Clostridia group as well as Proteobacteria, is believed to be behind the decrease of Bacteroides phyla, hence decrease the Microbial ecosystem.[127] As decrease in SCFAs-generating bacteria is crucial for dysbiosis, gut mucosal inflammation as well as loss of intestinal barrier integrity, it becomes significant to know dietary patterns manipulate the generation of the main gut bacteria metabolites.

Role of SCFAs-Dietary composition and Gut Bacteria Metabolites

In the absence of gut bacteria it would become impossible to degrade nondigestible. Dietary nutrients, particularly plant derived dietary fibres. These complicated carbohydrates are made up of the resistant starch, oligosaccharides as well as non starch polysaccharides that are utilized by gut bacteria in the form of energy substrates for forming *via* fermentation, SCFAs, especially acetate (C2), Propionate (C-3), Butyrate (C-4) as well as lactate.[116] Intake of fermentable, nondigestible carbohydrates give a lot of advantageous actions, varying from reduced chances of colorectal cancer as well a s amelioration of T2DM.[114,128] Though advantages of SCFAs have been shown by various modes (like histone deacetylase (HDAC) inhibition), SCFAs need to be thought to be immunoregulatory metabolites, especially the regulatory T-cells (Treg),[129] as well as crucial actors in the crosstalk among gut as well as immune system. That way SCFAs aid in immunosurveillance by their bonding to the metabolite-sensing GPCR like GPR41, GPR43 as well as GPR109A, that are abundantly expressed on immune cells.[129] Like Butyrate can work as immune messenger by its ability to stimulate T-cells to form IL-10 *via* GPR109A activation, hence repressing carcinogenesis by producing antiinflammatory actions (like colon inflammation).[130] This 2nd messenger action of SCFAs also involve the control of gene expression, improving glucose metabolism, cholesterol formation along with gut liberation of hormones like PYY as well as GLP1.[131] Fermentation of nondigestible carbohydrates as well as SCFAs synthesis also regulates brain function, knowing that butyrate can cause neuroprotective action as well as improve cognitive function,[132] along with propionate decrease activation of brain areas) like caudate and nucleus accumbens), that are implicated in reward processing in healthy people asked to look at pictures of palatable food items.[133] Emphasizing is the effect caused by certain bacterial species as well as their association with dietary patterns is the part played in immune homeostasis along with gut health by *F. Prausnitzii*. It has capacity to colonize human intestine that relates to the intake of dietary fibres,[134] as well as the expansion of *F. Prausnitzii* is also of crucial significance for its ability to generate butyrate,[135] whose involvement in various neurological as well as psychiatric disorders is always getting examined.

Depression as well as SCFAs

Lot of evaluation of microbial dysbiosis as well as change in bacterial composition in cases having depression has shown the presence of a major switch towards enhancing of bacteroides as well as a proteobacteria phyla as well as less than in healthy cases proportion of the Firmutes phyla that includes *Lachinospiraceae* as well as *Ruminococcaceae*, that has a crucial part in SCFAs synthesis.[136] Once Fecalibacterium is present it demonstrates a tendency on decrease the severity of depression like symptoms along with excessive amounts of Enterobacteriaceae escalates in depressed patients. Butyrate generation is the most significant connection among diet, SCFAs as well as psychiatric disorders. Actually inspite of its organic make-up, butyrate has the capacity of inhibiting strongly classes I as well as IIa HDAC action,[137] as well as inhibition of histone acetylation has been demonstrated to counteract depression–like behaviour in preclinical animal models.[138] These observations concentrate on the alterations of gene transcription *via* the changes of chromatin structure through modifications as well as DNA methylation have shown that epigenetic modes as well as chromatin remodelling can give promising other methods to usual antidepressive therapy like selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCA), or MAO inhibitors.[139] Mainly the evaluation of chromatin remodelling has aided in unravelling the modes *via* which environment (diet, stress as well as drugs of abuse) can generate alterations in gene expression. Hence histone acetylation gets facilitated *via* histone acetyl transferases (HATs) as well as correlated with enhanced access to transcription machinery as well as gene expression, while decreased transcription as well as gene repression get stimulated through absence of histone acetylation as well as HDAC-stimulated escalation of ionic crosstalk among histones as well as DNA, markedly condensed chromatin as well as densely packing of DNA.[140] Significantly, valproic acid (VA), that is a mood stabilizer having neuroprotective as well as antidepressant potential,[141] along with SCFAs as well as HDAC inhibitory action.[137] By prevention of withdrawl of acetyl groups through histone proteins, the HDAC inhibitors prevent histone acetylation, hence activation of gene transcription. HDAC inhibitors appear to extend onto same neurotrophic factors thought to be respon-

sible for neuroplasticity as well as depressive disorder along with HDAC downregulation has been correlated to the effectiveness of antidepressant therapy (like imipramine) in the social defeat stress model of depression.[142] Especially antidepressant therapy can prevent social defeat–stimulated BDNF downregulation within the hippocampus as well as PFC,[143] as well as HDAC inhibitors like VA as well as sodium butyrate can upregulate BDNF expression along with protect midbrain dopaminergic neurons.[144] Following oral delivery, butyrate can cross blood brain barrier (BBB), as well as work in the brain in the form of HDAC inhibitors, and shown *via* escalation of neuronal histone acetylation along with induction of neurogenesis.[145] Both antidepressant-like action as well as enhancement of hippocampal histone H4 acetylation has been seen following continuous delivery of sodium 6 butyrate,[146] as well as normalizing hippocampal BDNF expression, histone H3 acetylation, along with reduce chronic restraint stress stimulated depressive behavior.[147] Significantly, besides demonstrating antidepressant potential butyrate delivery also liberated *F. prausnitzii* species that, has demonstrated to cause equivalent antidepressant actions against chronic unpredictable stress (CUS)-stimulated depression –like behaviour in rats.[148] Further *F. prausnitzii* delivery restored an anti-inflammatory environment *via* enhancement of plasma amounts of interleukin-10 (IL-10) as well as avoiding the enhanced stress-stimulated liberation of pro-inflammatory C-reactive protein along with IL-6.148 Additionally to the well-known association among antidepressant treatment as well as BDNF expression in hippocampus along with prefrontal cortex (PFC) of depressed patients,[149] MAO deficit is thought to be the major explanatory posit of depression pathophysiology as well as subsequently SSRI,SNRI as well as MAO inhibitors being the main treatment agents. A reciprocal association appears to be present among serotonin transmission as well as BDNF expression, by which BDNF aids in serotonin neuronal differentiation, formation as well as function, as well as potentiation of serotonin signalling (like SSRI50 delivery) propagates neural as well as astrocytes BDNF expression.[150] The antidepressant action of butyrate delivery appears to have the same control among BDNF expression as well as serotonin neurotransmission mutually. Thus various HDAC inhibitors with butyrate facilitates cell differentiation through the potentiation of serotonin-stimulated BDNF gene expression,[151] as well as butyrate delivery was demonstrated to counteract CUS-stimulated anhedonic symptoms through the escalation of serotonin brain amounts along with reversal of serotonin amounts along with reversal of CUS -stimulated BDNF expression.[152] That SCFAs have a role in neuroplasticity, neurogenesis, consolidation of long-term memory as well as the sustainance of BBB integrity,[145,153] gives further corroboration to the fact that butyrate as well as SCFAs liberating bacteria might be advantageous dietary formed neuroprotective as well as antidepressant compounds. Significantly, besides butyrate, propionate also has a protective effect over microbial infections as well as oxidative stress (OS) stimulated escalation of BBB permeability.[154] Actually, the capacity of SCFAs to give protective effect against impaired MBC as well as deranged BBB integrity is very significant for preserving the main defensive structure of the brain as well as act against NPD pathogenesis. Lastly ,the alteration of bacterial community as well as escalation of valeric acid synthesis has been detailed in positive association with depressive symptoms,[155] SCFAs which can influence neurotransmitter liberation like glycine or adenosine receptors,[156] that with antagonistic effects might possess antidepressant actions (Table 2).[157]

Table 2. *Role of 5-HT- Dopamine and n3PUFA in NPD's*

Author/s	Ref. No	n-3 /6PUFA	ProResolving Mediators (PRM)	Neurotransmitters (Serotonin (5-HT), Dopamine [DA])	NPD
Skosnik et al	92	n3 generated, n-6 generated	RV's,PD's,MaR Eicosanoids (PG's,prostacyclins, TX's, LXs, LT)		SCZ
Zheng et al	93		Phospholipid turnover aberrant	COX2 inhibitor celecoxib->advantage	SCZ patients
Grosso et al	94	n3 generated	And eicosanoids might inc DAergic neurotransmission	And eicosanoids might inc DAergic neurotransmission	Refractory Depression And ASD+SCZ
Tamiji et al	95	Same-lipid metabolism	Same	Same	ASD
Hoen et al	96		Inverse relation of dec peripheral &brain DHA levels		Severity of SCZ
Montenos-Rueda et al	97	Suggested n3PUFAinvolvement – deficient in RBC's			SCZ Neuropath Ology
Chalon	98	n3PUFA deficiency	Dec of DHA content	Altered DA levels like in	SCZ Patients
El Sayed et al	99	n3PUFA dietary supplementation		Dec behavioral deficits,Cytokine Release+escalated antipsychotic and Celecoxib drug therapy	amphetam Ine induced SCZ-like Behavior (preclinical Model)
Sublette et al	100	n3PUFA status imp in prenatal/ early postnatal deficits	Brain deficiency	Might change DA receptors in ventralstriatum and Causehypofunction of mesolimbic DA system+ anhedonia	Seen in depre ssion-hence sig of n3PUFA status-an tenatal -studies role of PUFA's in major depre ssive disorders (MDD)
Camardes et al	101			Availability of DAT in depressed pts With/without anhedonia	A-I-N-w-fluoro Propyl-carb omethoxy -3β-(4-iodo Phenyl) tropane SPECT study

Grace AA	102		Dysregulation of DA System	SCZ NeuropathOlogy
Du Bois et al	103	Diff FA's SFA Diet n3PUFA diet	Variable effects on 5-HT neurotransmission-dec 5-HT2A and 5-HT2C receptors binding dec in mamillary nucleus(inf hypoth area) of rats Dec 5-HT2Aturnover binding in mamillary nucleus, 5-HT2C receptors binding in PFC & 5-HTT	n3PUFA intake-main actions on 5-HT function (receptors binding Binding and transporter Implications in NPD
Eisenhofer et al	104		Lot of tyrosine hydroxylase insmallintestine	DA synthesis
Xue et al	105	Antibiotic induced GM depletion	Dec int DA synthesis in mice	GM inhibit peripheral Invariant T cells
Diaz-Heitz et al	113	GF mice	Unequal brain mRNA expression of DA D1receptor (D1R)	Upregulation in hippoca mpus-dec in dorsal+ventrsa al striatum of GF mice
Nishino et al	106		Imbalance between DA and metobolitelike HVA and DOPAC+dec DA+5-HT turnover	GF mice
Crumeyrolle-Arias et al	107		Same Esp dec HVA/DA ratio-points to dec DA turnover	GF rats
Sher et al	108		Esp dec HVA/DA ratio-points to dec DA turnover	CSF In MDD
Hoban et al	109	Antibiotic induced dysbiosis	DecL-3,4-dihydroxy phenulalanine (L-DOPA in PFC+hippocampus L-DOPA+ HVA in amygdala)	Emphasis on brain DA amt ,turn over, Metabolism linked toGM
Yuan et al	110	n3PUFA deficiency alterfecal MICROBES		
Cocurello et al	111	AAPassoc dysbiosis		Atypical antipsychotics In SCZ patients Hence variable clinical effectiveness of AAP- with severe side Effects
Robertson et al	60	n3PUFA &GM-tight control in maternal env	Deeply rearrange offspring GM	Deeply rearrange offspring GM-GM in mice-long-term protection conferred Depletion causes dec Akkermansi a.muciniphilia
Robertson et al	112	n3PUFA gestational deprivation		Dec SCFA generation In mice
Cardoso et al	114	n3PUFA deficiency	Dec mesocorticolimbic DAergic and Striatonigral BDNF expression	Imp of diet lipids+Gut Generation of catechola Mines+NPD pathogene Sis Emphasis on modulation-Of ENS[102]
O'Mahoney et al	33	GM preservation	DA, 5-HT-preserve GM-essential for MBC-communication	both DA, 5-HT-key players in depression&SCZ

Dysbiosis as well as Neuroinflammation in ASD as well as SCZ-SCFAs

On 1st glance the pathophysiological association among Autism Spectrum Disorders (ASD) as well as changes in GM community appears very astonishing. However, definitely such association is present as well as probably depicts the biggest e.g. of the aftermath of deranged MBC for the pathogenesis of NPDs. ASD is a difficult neurodevelopmental syndrome to fathom influencing lot of behavioural aspects (like social interaction, motor stereotypes, self injury) along with communication significantly. The pathophysiological association among MBC as well as ASD gets corroborated by lots of GI disorders in ASD patients. More proof is derived from the association among the severity of the clinical signs of ASD as well as the exaggeration of GI symptomatology like abdominal pain, bloating along with constipation as well as/or diarrhea.[158-160] Of the 1st posit of comorbidity among ASD as well as GI disorders, a significant publication,[161] where low-grade intestinal inflammation (like stimulated by *Clostridium tetani*) was believed to have an etiological part in ASD pathogenesis. Further lot of studies supported the presence of lower Bacteroides to Firmutes ratio along with escalation of Clostridium in autistic children[162,163] as well as pyrosequencing analysis aided in isolation of the bacterial genus Desulfvibrio as present in greater numbers in autistic

as compared to non autistic patients.[164] Usually the Proteobacteria phyla gets over expressed in children having ASD, especially, those possessing mental retardation (MR),[165,166] as well as its spreading is commonly correlated with IBS, gut inflammation, as well as LPS generation.[164,167] LPS stimulated endotoxaemia induces changes in social behaviour in the offspring, even in prenatal immune challenge.[163] Regarding dietary therapy intervention, probiotic administration having a pool of various strains of Lactobacillus, Bifidobacterium as well as Streptococcus has been illustrated to decrease the Bacteroides to Firmutes ratio along with genus Desulfvibrio. Further than the drastic bacterial changes in the gut of children with ASD, other gut produced metabolites like free amino acids (FAA) secondary to proteins as well as peptide hydrolysis, have been correlated with ASD along with are higher in autistic subjects.[168] Of the lot of animal models of ASD, it has been seen that administration of Bacteroides fragilis in the offspring produced by the model of maternal immune activation (MIA) markedly re-equilibrated, microbial ecology, decrease gut permeability as well as ASD–like behaviours like social communication as well as anxiety.[169] Conversely, SCFAs might possess markedly separate actions in ASD pathogenesis. Greater than normal amount of PPA, BA, as well as valeric acid have been documented in autistic subjects.[170] These aberrant amounts might be at least partially be secondary to the imbalance regarding particular bacterial population in ASD like Clostridium, Bacteroides as well as Desulfvibrio that all represent critical SCFAs generators, especially PPA.[168] Thus physiological amounts of PPA have a part in the modulation of the immune function, gene expression, as well as mitochondrial along with lipid metabolism.[171] Aberrant generation or escalation of PPA propagates neuro inflammation *via* the liberation of pro inflammatory cytokines as well as gliosis by exaggerated proliferation of glial progenitor cells along with impairment of neuron/glia ratio as documented in ASD subjects.[172] Significantly, exposure to PPA in juvenile as well as adult rats has been formed in the form of a model for autism for reproducing autism-like brain changes (like neuro inflammation as well as oxidative stress) along with abnormal behaviours like repetitive dystonic movements, hyperactivity as well as deficit along with social interaction.[173] Aberrant PPA blood collection is also seen in the clinical problem called propionic acidemia (PA), where the fault of catabolism of branched chain amino acid (namely the action of enzyme propionyl CoA-Carboxylase, PCC), causes mitochondrial collection of propionyl CoA as well as mitochondrial dysfunction.[174,175] Similarly impairment of mitochondrial function in seen in patients of autism along with animals receiving icv PPA exposure.[176] Though dietary factors might have a crucial part in deciding the GM community, our insight regarding probable dietary interventions of modulating gut bacteria phenotypes is still not enough. Significantly a recent study didn't observe significant correlation among dietary patterns, fecal microbiota composition as well as alterations in social deficit in ASD children.[177] However in the same study, the consumption of particular healthy or unhealthy dietary patterns, was seen to manipulate the main incidence of selected either beneficial or harmful bacterial taxa along with SCFAs generation. Of the various dietary interventions/targeted nutritional methods pointed to be potential therapies in ASD, the gluten free/casein free (GF/CF) diet, the ketogenic diet as well as probiotic administration have been markedly evaluated.[178]

Just like ASD children, in other NPDs like SCZ as well as bipolar disorders (BD) a marked change in GM populations as compared to healthy subjects occurred. Higher amounts of bacteria from the Lactobacillus group was detailed in a study concentration on patients with 1st episode psychosis, that was seen to be associated with severity of positive symptoms.[179] Further in same study, over representation of Lachnospiraceae as well as Ruminococcaceae families was seen to be associated with severity of negative symptoms.[179] As per a later research,[180] SCZ patients demonstrated decreased microbial diversity of the gut flora with an enhanced chance of Lachnospiraceae, Bacteroidaceae as well as, Streptococococcaceae microbial species along with linear association with symptoms severity. As probiotic administration can enhance BDNF amounts as well as probiotics re-establish hippocampal expression following social stress,[38,181] the association among SCFAs generation as well as BDNF function might have a main key significance for the influence of GM in SCZ pathogenesis. Potent implication of BDNF in SCZ,[182] appears from lot of function's of this neurotrophic factor (NF) like its significance in brain generation, neural differentiation, neurotransmitter liberation, neuronal plasticity, cognitive alterations protection as well as survival of dopaminergic, 5HT, as well as cholinergic neurons.[183] Antibiotic therapy of GF mice displayed changed BDNF expression in various brain areas implicated in SCZ, that include hippocampus as well as cingulate cortex.[8,184] As seen for the part of SCFAs in depression, butyrate can normalize BDNF expression along with depression like behaviours in animals,[147] *via* modes implicating BDNF-5HT synergistic modulation as well as HDAC inhibition as well as potentiation of 5HT transmission.[151] Besides butyrate supplementation stimulating recovery of BDNF expression as well as memory disturbance,[185] its action as HDAC inhibitor gives proof for mode for its capacity of suppressing various LPS stimulated pro inflammatory factors,[186] that are known parts of SCZ pathogenesis.[187] Significantly stress-stimulated impairment of GM diversity as well as alterations in brain BDNF expression are correlated with the changes in NMDA receptor subunits, like for the reduction of Glu N2A subunit in the hippocampus as well as cortex of germ free (GF) mice.[22] The decreased function of NMDA receptor is believed to be one significant posit in SCZ pathophysiology,[188] as well as sporadic mutations of the GR1N2A gene that encodes the Glu N2A subunit has been reported in both SCZ as well as ASD patients.[189] Prebiotic administration, as fructo-oligosaccharides (GOS), besides facilitating hippocampal BDNF escalation, further enhanced the expression of BDNF Glu N2A subunit, hence giving further proof that prebiotics–based Bifidobacteria proliferation promotes the expression of certain NMDA subunits.[181] Further fecal microbiome transplantation from SCZ patients to GF mice formed aberrant hypothalamic GABA as well as glutamate enhancement, simultaneous glutamatergic hypofunction as well as SCZ like behaviours.[180] Regarding BD, a recent comparative evaluation of the stool microbiome of patients with BD, emphasized a main reduction of the phylum Firmicutes, as well as especially of the BA–generating Faecalibacterium.[121,190] whose supplementation has shown potential antidepressant–like actions,[148] as well as whose deficit in GM is thought to be a marker of severe inflammatory clinical problems like CD (Table 3).[134]

Table 3. *Association of GM changes and Diet SCFA 'sin Depression*

Author/s	Ref. No	GM	SCFA	Inflammation	Enzyme Changes	Neurotransmitter	NPD
Jiang et al	135	Shift to> Bacteroides &Proteobacteria <than healthy subjects-Firmicutes dec –incl Ruminococcacea and Lachnospiraceae	Sig for SCFA prodn				sec to >desaturation SFA to,MUFA+dec brain energysupply
Zhang et al	136		Butyrate-imp		Inhibits Class I&IIa HDAC activity		Sig in psychiatric disorders
Valvassori et al	137		Na Butyrate		Inhibition of histone acetylation	Inc BDNF and Cognition in models of maternal deprivation &Chronic mild stress	Antidepressant Counterat depression-like behavior (preclinical models
Tsankova et al	138		n by chromsatin str by h		Changes ingene transcription by chromsatin str by histone modification+DNA methylation		Give alternate options to Usual antidepressants like SSRI,SNRI. TCA,MAOinhibitors
Herre et al	139				Chromatin remodelling		Given modes by which environ(diet,stress ,drugs)cause changes in gene expression
Machado-Veira R et al	140			Valproic Acid+ Butyrate		HDAC inhibitor	Mood stabilizer+neuroprotective
Tsankova et al	141				Mood stabilizer+ neuroprotective	NF's dec prevented by HDAC inhitors-thus activate gene transcription	HDAC inhitors associated with effectiveness of imipramine like antidepress in social defeat stress modelof depressio
Zhang et al	142					BDNF downregulation in hippocampus &PFC	Esp social defeat assoc-improved with antidepressants
Wu et al	143				HDAC Inhibitor (VA and Sod butyrate)	Upregulate BDNF expression+protect midbrain DAergic neurons	
Braniste et al	144				Butyrate crosses BBB-oral-act as HDAC Inhibitor in brain		Incr histone acetylation and neurogenesis
Yamawak et al	145				Rpted Butyrate admn	Inc hippocampal histone H4 acetylation seen	Antidepressant potential
Han et al	146					Normalization of hippocampal BDNF expression, histone H3 acetylation	Dec inchr Restraint stress-induced depressive behavior
Hao et al	147	Faecalibacterium Prausnitzii.(FP)	Produces butyrate		FurtherFP admn Reestablishes anti-infl environment(inc plasma IL10&prevent stress ind inc CRP +IL-6		Antidepressant like behavior in CUS-induced depressive Behavior
Yu et al	148					BDNF expression in hippocam-pus& PFC MAO deficiency–main explains	Antidepressant therapycorrelates Depression pathophysiol-ogy –thus antidepressants like SSRI,SNRI. TCA,MAOinhibitors work
Martinowich et al	149					Reciprocal control among BDNF expression and 5-HT transmission Aids in neural+astrocyte BDNF expression	Thus BDNFaids I n5-HT-neuron differentiation,,dev &function+potentiate 5-HT signaling-thro SSRI

Morita et al	150		HDAC Inhibitor	Promote neurosteroid Mediated cell Differentiation+inc n5-HT-induced	BDNF gene expression In rat C6 glioma cells
Sun et al	151		Butyrate administration	Inc 5-HT- levels Reversed anhedonic symptoms in InCUS induced dec BDNF expression	InCUS-
Intlekofer et al	152	SCFA		Promote neuroplasticity Neurogenesis,consolidating long-term memory via BDNF-based mode	Supports that butyrate and GM generating SCFA-have role as dietary derived neuroprotective and antidepressants agents
Hoyles et al	153	Propionic acid		Also protects BBB and against microbial infection &inc permeability	Very sig in protecting from NPD pathogenesis
Szczesniak et al	154	Changes in GM		Inc in valeric acid-affects NT liberation	Causes depression
Wang et al	155	Same this SCFA-VA		This VA can influence NT release by acting on glycine or adenosine receptors	
Serefko et al	156			Synergistic effects of antagonism like caffeine & NMDA R ligands	Cause further inc antidepressant actions.

Table 4. *Correlation of Gut Microbiata (GM) with Neuropsychiatric Disease (NPDs)*

Author/s	Ref. No	Role of GM	Diseases-NPD/ IBD	Probiotics Effective	Role of Vagus	Neurotransmitter Change with Probiotic	Disease Influence
La Fata et al	18	+nt Candid albicans and streptococcusagsalactae	Brain Dis-depression,anxiety	++ L.Rhamnosus		GABA+DA-products of micr metabol	Socialstress,cognition Depression-DOPAC-Gut–brain module+ve assoc -QOL
Hasan Mohajeri et al	23	Gut microbiome changes Like altered Bacteroides :Fermicutes ratio	Influence Brain function	++ L.Rhamnosus	Present	Inccorticosterone,GABAAR mRNA-Cing cortex,decr GABABR-hippo,amygdale-inc GABAA inhippo	Antidepressant, anxiolytic
Brav oet al	6	Chr Lactobacillus Rhamnosus Intake	Marked decr anxiety stress assoc Corticosterone – blocked by vagotomy	Beneficial effect of L.Rhamnosus (JB-1)	+nt Vagotomy reverses benefit	Inccorticosterone,GABAAR mRNA-Cing cortex,decr GABABR-LR,hippo,amygdale-inc GABAA inhippo	Antidepressant, anxiolytic
Barrett et al	27	Human gut Derived Lactobacillus and Bifidobacteria were cultured			+nt with HPA-axis	Only to assess Their ability to convert MSG to GABA	Lactobacillus BrevisD6108 and Bifidobacterium dentium most efficient
Li et al	28	Inc Firmicutes		++ L.Rhamnosus+ Bifidobactlongum		+ve on Colonic 5FT metabol,neg on 5FT metabol-pfc	All neg changes reversed with probiotics in rat chr mild stress
Kelly et al	29	Faecal microbiota of Depressed pts	Depression	Faecaltransplantation, Microbial signatures transfer to animals		In rats free of microbes developed anhedonia and anxiety like behaviors	Depression like symptoms transfer
Zheng et al	30	Fermicutes, Bacteroides and actinobacteria abundant in MDD pts	Depressionpheno type in GF mice	Faecal transplantation from MDD pts worsened	-	GF mice Had >immobility in forced swimming test	Worsened depression
Wong et al	31	Decr Bifidobaand cte-rium species and incr Lactobacillius causing	Chronic stress			Inhibited NFKB induced inflammation and inflassome activation via IL-1β-liberation	
Valles-Colomer et al	32	Wide taxa kinds	Depressed pts-metagenomic study +16S rRNA gene evaluation	Decr bacteroides correlated with>depression chance			QOL decreased in depression pts

DISCUSSION AND CONCLUSION

The summary can be seen in Table 4 is showing a correlation of gut microbiata (GM) with neuropsychiatric disease (NPDs), Table 1 is showing GM, microglial activation, neuroinflammation and NPD's/brain alterations association, Table 5, is demonstrating role of fatty acids, GM changes and NPDs with emphasis on roles of EPA and DHA, Table 2 showing role of 5-HT-Dopamine and n3PUFA in NPD's and how n-3 generated eicosanoids increase dopaminergic neurotransmission and greater DA-D1 receptors, and help in controlling refractory depression, role of pro-resolving mediators along with alteration in serotonin metabolism and how gut DA and serotonin preserve MBC communication along with enhance striato nigral BDNF generation, Table 3, demonstrating association of GM changes and diet SCFA's in depression, empha-

Table 5. *Role of Fatty Acids, GM changes and NPDs*

Author/s	Ref. No	n-PUFA	GM	Inflammaton	SPM	Studies/TLR	NPD
Yang et al	53	n-3	Altered Possibly by alteration in FFA metabolism that influences glucose transport and indirect affect on GIT environment	Control via ALA	Then *via* EPA+DHA	SCZ cohort-have abn incSFA,MUFA+proinfl eicosanoids	sec to >desaturation SFA to,MUFA+dec brain energysupply
Serhan CN	54	n-3 derived	altered	Control by SPM	By SPM	Proresolving lipid mediators	
Bozzatello et al	55	n-3 derived	altered	Control by SPM	Lipoxins,resolvins,protectins,maresins	Dec n-3 PUFA in NPD	SCZ, BD, depression- EPA+DHA
Berger et al	56	n-6:n3 ratio	altered			In young subjects	Ultra high-risk for depression-Predicted-mood disorders
Kaliannan et al	57	n-6:n3 ratio	Inc fecal Enterobacteriaceae,inc proteobact and dec Bacteroides and Actinobacteria	Inc TNF-α, IL-1β,IL-6+LPS, int permeability (signs of chr infl)	Intention to study SCZ, ASD, MDD	Transgenic mice-could overproduce n-6 PUFA	Various cascades->metabolic endotozaemia,fatty liver +high fecal 1-methylnicotinamide,cysteine,spermidine(markers of gut dysbiosis +infl
Kaliannan et al	58	Same with n6 over expression as 57. With >n-3 expression caused→	Inc bacteroides, dec LPS levels, gut permeability and endotoxaemia	Antiinflammatory action of n3 overexpression	Same –how n3 PUFAs help in NPD	Transgenic mice-could overproduce n-6 PUFA	Confirmed 57 results and how > n-3 PUFA expression inc intestinal alk phosphatase(IAP)-
Portnoy et al	59	Indirect effects of n3 PUFA			Same	Family history of violence –R,double blind study	Dec aggression in children +adultcaregivers
Robertson et al	60	Inc n3 PUFA				Maternal supplementation	n3 PUFA environment – prime GM in early life-protect from HFD caused metabolic changes
Pusceddu et al	61	n3 PUFA EFFECTS	GM restored in maternally separated rats		Long-term EPA+DHA supplementation		Implicates n3 products can protect in mood disorder
Lin et al	62	n3 PUFA effects			Low EPA+DHA Levels in depresion	Meta-analysis on n3 in mood disorders	Depression pts
Pusceddu et al	63	n3 PUFA effects	Firmicutes: Bacteroides				Antidepressant effect still not well understood
Jory	64				Dec EPA+DHAlevels in ASD	Canadian children	ASD
Pawelczyk et al	65	n3 PUFA effects			Inc EPA+DHAlevels	Placebo controlled study in 1st episode SCZ –OFFER trial	Inc BDNF levels-inverse correlation with depressive symptoms
Rao et al	66	n3 PUFA deprivation					Dec BDNF in PFC-keyarea for SCZ+ASD pathophysiology
Yan et al	67	n3 PUFA effects		Antiinfl action via macrophage stmn+inhibition of NNLRP3 inflassomeactivation + IL-1β secretion		Mice fed	
Chassaing et al	68	Bacteroides Fragilis	Sense polysaccharide A on BF	Thus prevent systemic low grade inflammation		Role of TLR studied on immune cells and enterocytes	
Rakoff-Nahoum et al	69			Prevent activation of proinfl cytokines or NFχB mediated infl program		TLR recognize PAMP	Thus preserve intestinal homeostasis by dec entry of bact products to cytosolic inflammasome
Hug et al	70			Correlate with neuroinflammation		TLR s essential for gutimmune system	Maintain intestestinal homeostasis Dysreg of TLR->neutoinfl&NPD

Yun et al	71	Microbial perturbations	Astroglial and microglal activation, impaired neurogenesis +change in glutamate transmission and NMDA subunits		Seen in SCZ
Hwang et al	72	Microbial alteration +dietchanges-incr diet fat SFA-palmitic and lauric acid-Although n3 n-6PUF Amixed diet	Inc LPS signaling- inc TLR4 –related infl signalingacc to fat Might inc proinfl potential-just >MUFA but >SFA-reciprocal action of SFA & n3 PUFA	Disrupt TLR activation sensitivity, Activate TLR-mediatedinfl program n3 PUFA,esp DHA deactivate TLR4-TLR2-assoc infl program ,SFA can induce dimeriza-tion of TLR4&TLR2->translocation of these R's to lipid raft in plasma memb->inc downstream signaling	Inc risk of NPD Like SCZ+ASD -this inhibited by DHA
Raimondi et al	77	Dietary fats	Inc bile acid secretion along with bile acid mediated toxic signaling affect enterocyte tight junction proteins		Harmful action of SFA on int barrier function overtake that done by n6 PUFAenriched or n3 PUFAenriched HFD.

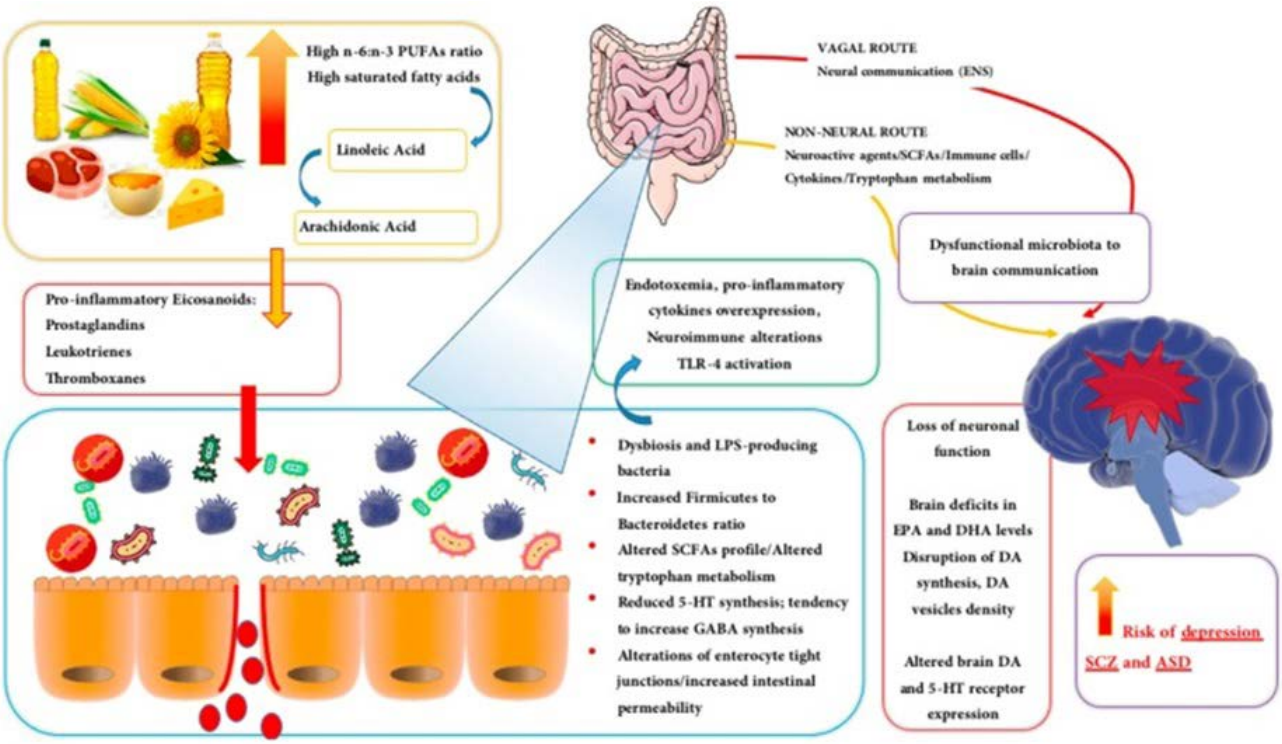
Table 6. *SCFA, Dysbiosis and Neuroinflammation with Neurotransmitters in ASD/SCZ/BD*

Author/s	Ref. No	GM	SCFA	Neuroinflammation and Gut Problems	ASD/SCZ	NT	Gut problems and Misc
Buie et al	158	Altered	NC	ASD-surprising that GM connection there ASD affects behavior-social interaction,motor stereotypes, self injury	ASD studied		Represents biggest eg of altered MBC for the pathogenesis of NPD
Ashwood et al	159	Altered	NC	Lot of abdominal distention ,bloating(constipation and/or diarrhea	same		Significant correlations of GI disorders
McElhanon et al	160	Altered	NC	Same	Meta-analysis		Same
Bolte ER	161	Clostridium.Tetani (CT)	NC	Low grade intestinal Inflammation due to CT			1st study to show ASD &GM correlated
Luna et al	162	Bacteroides :Firmicutes low &inc CT	NC		ASD		IN ASD
Finegold et al	164	Desulfvibrio Greater			In ASD than nonautistic		Pyrosequencing study of fecal M
Emanuele et al	165	Desulfvibrio liberates LPS	NC	Low grade Endotoxaemia supported thus by this gram negative anaerobe	In ASD		Esp severe ASD
Plaza-Diaz et al	166	Mostly Proteobac Teria overrepresented			In ASD		Mainly in MR Also shown by 163
Shin et al	167	Proteobac Teria spread	NC	Assoc with IBS,Gut Inflammation&LPS generation	In ASD		Also shown by 163
Suh et a	168	Desulfvibrio Interestingly Are sulfate reducing bact	NC	Thus sulfur amino acid (SAA) metabolism Defective-aberrant Sulfur urine excretion	In ASD		Explains defective immune function in ASD

Tomova et al	163	Probiotic supplemenation of Lactobacillus, Bifidobacterium ,Streptococcusdec Bacteroides: Firmicutes ratio with Desulfvibrio Prevalent	NC		In ASD		
DeAngeli et al	169		NC	Other gut derived metabolites like free AA due to protein/ peptide hydrolysis	Seen in ASD		GreaterIn ASDindividuals.
Hsiao et al	170	Supplementing Bacteroides Fragilis in	NC	Offspring of model of maternal immune activation(MIA)			Sig nificantly Requilibrates GM, decr gut Permeability and ASD-like behavior like social communication+anxiety
Wang et al	171		>noramts PPA,BA,Valeric acid				Seen in ASD
Lopetuso et al	172	Imbalance with main Clostridium. Bacteroides& Desulfvibrio Main producers of SCFA esp PPA			in ASD		
Rossignoi and Frye physiologi-cal PPA – modulates	173			While immune physiological PPA–modulates function,gene expression&mitochondrial &lipid metabolism			
Abdelli et al	174		Abnormal PPA-gen or inc	Neuroinflammation by proinfl cytokines&gliosis by inc glial progenitor cells& deranged neuron/glia ratio	in ASD		As documented in ASD
Schultz et al	175	SCFA	Exposure to PPA in juvenile and adult rats	Produces ASD–like brain changes Neuroinflammatio%oxidative stress	Inmodel of autism		
MacFabe DF	176		Abnormal PPA accumulation	Seen in clinical problem called Propionic acidaemia Sec to PCC enzyme			Causes mitochondrial collection of PCoA and mitochondrial Dysfunction
Berd-ing and Donovan	177	Role of diet –imp role in modifying GM-healthy &unhealthy bact taxa	SCFA generation	Intake of sp nutrients and nunhealthy diet			Social deficit seen in ASD Children
Doenas C	178	Targeted nutrition approaches		Potential gluten free/casein free diet,ketogenic diet	In ASD		Suggested as potential therapies for ASD and Probiotics studied deeply
Schwarz et al	179	Greater Lactobacillus Whileover expressionin same study of Lachnospiraceae, Ruminaceae		Corelated with positive symptoms corelated with negative symptoms	SCZ research		1st episode Psychosis
Zheng et al	180	Decr gut flora withgreater Lachnospiraceae, Bacteroidaceae &Streptococ-caceae		Linear correlation with symptom severity Fecal transplantation of GM from SCZ pts	SCZ	Modulates Inc Glutamate-Gluta-mine- GABAcycle	and SCZ like behavior in mice
Savignac et al	181	Prebiotic Feeding Further (FOS)&GOS Bifidobacteria prolif aids in NMDA R subunits		Inc hippocampal BDNF, in hippocampal GluN2A Subunit-more proof for	SCZ pathogenesis	Inc BDNF, NMDAsubunits and d-serine	After social stress,thus implication of SCFA and BDNF function in

Nieto et al	182			Strong involvement of BDNF, multiple functions in brain dev, neural diff, NT release, neuronal plasticity,cognitive changes ,protection+survival of	SCZ		
Numakawa et al	183	fer	fer	Neurogenesis, neural function of BDNF	SCZ	DAergic, 5 HT, Cholinergic neurons	Pathophysiology Of SCZ
Bistoletti et al	184	Antibiotic treatment of GF mice	Butyrate normalizesBDNF	Altered BDNF in Hippocampus,cingulate cortex	Areas implicated in SCZ	Altered BDNF	Just like depression[147] *via* BDNF-5 HT-synergistic control of HDAC inhibition +potentiate 5 HT transmission[151]
Barichello et al	185	In Pneumococcal meningitis	Butyrate Delivery	Reestablishes BDNF expression and promotes memory			
Chriett et al	186		Butyrate Delivery	Also acts as HDAC inhibitor-mode for suppression of LPS-induced proinflammatory factors			

Figure 2. *The Figure Sketches the Current Knowledge and the Potential Relationship between Consumption of n-6 PUFAs- and SFAs-rich Diets, Production of Pro-Inflammatory Eicosanoids Mediators, Derangement of Microbial Ecosystem and Increased Liability to Neuropsychiatric Diseases (NPDs)*



The prevalent ingestion of dietary n-6 PUFAs (and SFAs) is linked to the drastic alterations of microbiota diversity, inflamed microenvironment, overgrowth of harmful bacterial species (e.g., Enterobactericeae), metabolic endotoxemia (increased plasma endotoxins, such as LPS) and increased intestinal permeability. Besides the upregulation of cyclooxygenases- and lipoxygenases-dependent synthesis of eicosanoids, other mechanisms may contribute to dietary n-6 PUFAs/SFAs-induced dysbiosis, such as: 1) increased expression of NF-κB signaling pathway and induction of pro-inflammatory cytokines and 2) decreased synthesis of "specialized pro-resolving mediators" (SPMs) including the resolvins (RVs) series E (RvE) and D (RvD).The overall picture of systemic metabolic endotoxemia triggers immune dysregulation and recognition of pathogen-associated molecular patterns via toll-like receptors (TLRs) and in particular TLR4-dependent synthesis of pro-inflammatory cytokines (e.g.,TNF-α, IL-1β, IL-6, and IL-12). In turn, reduced 5-HT synthesis, altered tryptophan metabolism and SCFAs balance contribute to dysfunctional microbiota-to-brain-communication.The reported deficits in plasma and brain EPA/DHA levels may further contribute to the disruption of DA and 5-HT function and, ultimately, to increased risk of depression, SCZ and ASD.[34]

sizing on role of SCFA's, mainly butyrate in acting as HDAC inhibitors, enhance H3 and H4 acetylation and aid in increasing BDNF expression along with aid in decrease of dose of antidepressants like SSRI's and others and how drugs like valproic acid efficiency improves. Table 6 showed the role of SCFA, Dysbiosis and Neuroinflammation with Neurotransmitters in ASD/SCZ/BD where after boltes study showing increased Clostridium tetani correlated in intestines of ASD children, further studies on alteration in GM in intestine and association with ASF, SCZ ,BD and changes in BDNF expression with roles of butyrate and even propionic acid help along with abnormal SCFA isovaleric production harms .

Globally with the change in dietary habits with prevalence of western diet incidence of obesity, type 2 DM not only have markedly increased but so have incidence of depression along with neuropsychiatric disorders like anxiety, IBS, etc. Currently, we have atleast 4-5 patients who have got all investigations like endoscopy, EEG, EMG and gone from pillar to post yet no answer got with neither her gastric troubles get sorted out nor the so called label of psychosomatic disorders for which patients are loaded with use of drugs like clonazepam, other antianxiety drugs and it all simply gets explained by the changes in neurochemicals like GABA, DA serotonin as emphasized in this article so need for changing diet habits back to our Indian type diets typically is emphasized or Mediterranean diet instead of the Western diet . GM community can be drastically changed with dietary fats, in either side *via* lipids of various kinds. Above we have reviewed how SFA can cause dysbiosis as well as chances of NPD formation, as well as selected lipids like (n-3 PUFAs)along with their metabolites can aid in disease resilience/resolve the basic systemic as well as brain inflammation implicated in SCZ, ASD as well as depression pathogenesis. Whereas extensive proof corroborates the thought that aberrant escalation of n-6: n-3 ratio is a main pathogenetic connection among dietary lipids of NPDs (Figure 2), results showing a disturbing link among n-3 PUFAs amounts, GM diversity as well as SCFAs generation.[191] In A population dependent study, greater circulating amount of DHA were observed to positively associate with greater microbiome diversity as well as greater amounts of Lachnospiraceae family, irrespective of dietary fiber intake. Knowing that *Lachno spiraceae* family is one significant SCFAs generator, this study points to a potential extra mode, underlying the connection among n-3 PUFAs, GM health as well as lower chance of NPDs. Similar proof on depression like behaviors produced in mice *via* social isolation were seen to correlate with a switch in GM composition, besides a reduction in SCFAs generating bacteria (like Allobactum) that was sensitive to dietary DHA intake.[192] In this review lots of correlations that interrelate imbalanced intake of selected dietary FAs towards the chances of NPDs. By utilizing this current insight into the association of dietary lipids, disrupted GM population as well as alterations in neuroactive substances (especially DA as well as 5HT) one might enhance our understanding regarding NPD pathogenesis as well as design innovative therapeutic methods along with forming NPD related biomarkers for getting early diagnosis as well as personalized medicine.

INFORMED CONSENT

No institutional consent needed although we are running our independent center's all 3 authors and this review article does not involve testing any medicine on any subjects or animals hence no consent needed although our ethical committee does approve.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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The Effect of L-Carnitine, Green Tea Extract and Lotus Leaf Extract on the Body Fat Percentage in High Energy Diet-Induced Obese Rats

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ABSTRACT

Background
Obesity has become a public health issue of global concern. Obesity is often associated with the occurrence of many diseases, and will also increase mortality; it not only affects personal health, but also increases healthcare costs, thus reducing social productivity and causing negative social and economic impacts. Therefore, ameliorating obesity is an issue worth attention and effort. The development of a natural and safe anti-obesity combination is worthy of further research. It is known that L-carnitine, green tea and lotus leaves have anti-obesity potential, but there is no research and discussion on this novel combination to improve body fat.

Objective
This study explored how the dietary supplement formula containing L-carnitine, green tea extract and lotus leaf extract (CGL) lowered the body fat accumulation in rats induced by high-energy diet.

Design
The test used 60 male Sprague Dawley® white rats aged 6 weeks, which were first divided into the control group (12 rats were given normal feed) and the experimental group (48 rats were given high energy diet; HE). The HE group was further divided into H_2O and CGL groups (296, 593 and 1186 mg/kg, to be designated as CGL-L, CGL-M, CGL-H respectively). The rats were first fed with feed for five-weeks, and then fed with different doses of CGL by gavage starting from the sixth-week. After nine-weeks of feeding, the rats were sacrificed to obtain their body weight, feed intake, body fat, serum biochemical indices and liver lipid measurements.

Results
The results show that the final body weight of HE+CGL-L (578.8±41.6 g) was significantly lower than that of HE+H_2O (634.9±42.2 g), and the body fat amount of HE+CGL-L (36.6±9.8 g) was significantly lower than that of HE+H_2O (49.4±13.8 g). Feed efficiency and calorie efficiency of HE+CGL-L were also significantly lower than that of HE+H_2O (p<0.001). HE+CGL-M and HE+CGL-H were also able to significantly reduce the final body weight, body fat amount and serum-free fatty acid concentration (p<0.05).

Conclusion
CGL can significantly reduce the final body weight, body fat amount, body fat ratio, feed efficiency and calorie efficiency. CGL has the potential as a new dietary supplement for weight loss. However, the significance of these results on humans taking the supplement for prolonged periods of time is unknown and should be a focus for future investigations.

Keywords
Obesity; L-Carnitine; Green tea extract; Lotus leaf extract; Weight loss.

INTRODUCTION

Obesity is a global concern. According to the estimation of the World Obesity Federation, the global number of overweight or obese adults will increase from 2 billion in 2014 to 2.7 billion by 2025. Obesity control is a major challenge to global public health. Compared with healthy people, obese people are more likely to suffer from diabetes, metabolic syndrome, dyslipidemia,

hypertension, cardiovascular disease, knee arthritis, etc.[1-3] In order to prevent the occurrence of obesity, dietary ingredients can also help to improve lipid metabolism, control body weight, and reduce fat deposits.

L-carnitine can help transport fat into mitochondria for energy metabolism. Contradictory outcomes have been observed in previous studies: some studies found that non-obese healthy people who took L-carnitine did not lose weight[4,5]; however, the results of the meta-analysis of the database show that it did affect weight loss, with the mean weight reduction being 1.33 kg and body mass index (BMI) reduction 0.47 kg/m^2. [6]

Green tea contains lots of antioxidant substances, such as catechins and tannins. Green tea can suppress oxidation in a dose-dependent manner, and its resistance to oxidation is six-fold than that of black tea.[7] Previous studies confirmed that green tea is rich in catechins, which can regulate blood lipids, promote metabolism and reduce weight.[8] An adult who drinks green tea containing 583 mg of catechins every day can reduce BMI, body fat, waist circumference and hip circumference.[9] In a 12-week experiment, drinking 625 mg of catechins daily in combination with moderate intensity exercise, three times a week could eliminate abdominal fat and reduce the blood concentrations of fatty acids and triglycerides,[10] which confirms the effect of catechins in green tea on weight loss.

Leaves of lotus (*Nelumbo nucifera*) have many medicinal uses in traditional culture. Various pharmacologically active substances can be extracted from different parts of lotus plants, such as nuciferine, flavonoids, polyphenols and glycosides,[11] and they have numerous effects, such as anti-obesity[12] and cholesterol reduction.[13]

The purpose of this study was to explore how a new formula, a dietary supplement containing L-carnitine, green tea extract and lotus leaf extract (CGL), helped reduce body fat accumulation by using the model of Sprague Dawley® rats fed with high energy diet to induce body fat accumulation.

MATERIALS AND METHODS

Supplement Composition

Each tablet (717.06 mg/tablet) of compound plant-based supplements provided by HealthTake Corporation contains L-carnitine, green tea extract (80 to 120 mg of catechin per tablet) and lotus leaf extract.

Study Design

The animal experiment project was reviewed and approved by the Institutional Animal Care and Use Committee of China Medical University (approval ID: CMUIACUC-2018-241) and was carried out according to the institutional animal ethics guidelines of the China Medical University. 60 male Sprague Dawley® rats aged 6 weeks were purchased from BioLASCO Taiwan Co., Ltd., which were raised at the Animal Laboratory of China Medical University. The temperature of the Animal Laboratory was set at 22±2 °C, and the light was on for 12 h and off for 12 h (light on at 8 AM, and off at 8 PM). After a week of acclimation, the experimental group began to be given high energy diet. The high energy diet (5.24 Kcal/g; 20% protein, 60% fat, 20% carbohydrates) was imported feed (D12492, Research Diet Inc., New Brunswick, NJ, USA). The control group was given normal (2.85 Kcal/g; 24% protein, 11% fat, 65% carbohydrates) imported feed (maintenance diet/Altromin 1320, Altromin Spezialfutter GmbH & Co. KG, Im Seelenkamp, Germany), and the drinking water was treated with high-pressure sterilization.

The experimental animals were divided into the control group with 12 rats and the high energy diet (HE) group with 48 rats.[14] Control group was fed with normal feed, while HE group was fed with high energy diet. In the first 3-weeks, three rats were housed in one cage, and from the fourth-week to the ninth-week, every rat had its own cage to facilitate the measurement of food intake and feed efficiency. After having been fed with high energy diet for five-weeks, control group continued to be fed with normal feed; HE group was divided into four groups, each with 12 rats: with and without CGL. One group was given sterilized water (HE+H_2O). The oral dose of rats was calculated based on the recommended daily intake of CGL for humans (4 tablets, each 717.06 mg) and the metabolic conversion ratio of 6.2 between humans and rats. The daily dose of rats was 2868.24 mg/60 kg (human body weight)×6.2=296 mg/kg; 296 mg/kg is equivalent to one time the human body dose. The daily doses used in this experiment were 296, 593 and 1186 mg/kg, which are one, two and four times the human doses, to be designated as HE+CGL-L, HE+CGL-M and HE+CGL-H, respectively. The samples were prepared as suspensions of 29.6, 59.3 and 118.6 mg/mL by adding deionized water. The rats were fed by gavage once a day, and the volume given was 1 mL/100 g body weight. After 4-weeks' feeding, the experimental animals were sacrificed after the feeding was stopped for one night. Blood was collected from the celiac artery for blood biochemical analysis when the rats were under anesthesia, and epididymal, perirenal and mesenteric adipose tissue in the peritoneal cavity was removed for measurement of its precise weight and calculation of body fat ratio (%).

Body Weight and Food Intake

The rats were weighed once a week during the experiment as the basis for administering the weekly amount of test substances. The weights of the rats at the beginning and end of the experiment were compared. The daily feed intake was recorded from the fourth-week to the ninth-week to calculate each rat's average daily feed intake. At the end of the experiment, the feed efficiency during the four-weeks of administering the test substances was calculated as follows: Feed efficiency (%) defined as (weight gain/food intake)×100.

Calorie Intake

Food intake was converted into calorie intake. The normal feed was calculated at 2.85 Kcal/g, HE was calculated at 5.24 Kcal/g, and CGL was calculated at 3.9 Kcal/g. At the end of the experiment, the calorie efficiency was calculated; Calorie efficiency (%)

defined as (weight gain / calorie intake) × 100.

Measurement of Liver Lipid Concentration

After the blood was collected from the celiac artery, the liver was washed with saline solution, and then stored at -80 °C until further analysis. After lipid extraction was done, the concentrations of liver triglyceride and cholesterol were measured.[15] We took 0.1 g of liver tissue, added 2 mL of extracting solvent (chloroform : methanol=2:1), and then homogenized it with a homogenizer. We let it stand at room temperature for 60 min before centrifuging it at 2200 xg for 5 min. We took the supernatant and placed it into a clean 1.5 mL centrifuge tube, added 0.2 mL 0.9% NaCl and mixed it well; at this moment the solution appeared white and turbid, centrifuged it at 300 xg for 5 min to make it separate to two layers; kept the bottom layer in an oven to be blown-dry with nitrogen at 55 °C; after drying, added 100 μL solvent (tert-butyl alcohol: triton X-100: methanol=2:1:1), heated to dissolve it at 65 °C for 15 min, and then tested with commercially available cholesterol and triglyceride reagents (Roche, Switzerland).

Measurement of Serum Biochemical Properties

After the blood was collected, it was centrifuged at 2000 xg for 15 min to acquire the blood plasma for biochemical analysis. The concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglyceride, uric acid, creatinine were analyzed by using commercial kits (Roche, Germany) and evaluated by biochemical analyzer (COBAS MIRA PLUS, Roche, Switzerland). Free fatty acid was determined by using a non-esterified fatty acid kit (RANDOX, County Antrim, UK). Total cholesterol, low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), sodium and potassium were determined by using commercial kits (Fortress Diagnostics Limited, Antrim, United Kingdom). Ketone body was determined by β-Hydroxybutyrate (ketone body) colorimetric assay kit (Cayman Chemical, MI, USA). Blood glucose levels was measured using a CareSens blood glucose meter (i-SEN, Korea).

Statistical Analysis

Results are expressed as the mean±SD. All experimental data were analyzed by one-way analysis of variance using the Dunnett's test, provided the data passed a normality test. A value of $p<0.05$ was used to indicate statistical significance between groups.

RESULTS

Body Weight Changes

As shown in Table 1, the initial weight of rats in the control group was not different from that of the rats in the four HE groups. The weight of rats in the HE+H_2O group was significantly higher than that in control group from week-1 to week-9. When the rats in the HE feed group had been fed for 5-weeks, there was no difference in the average weight of the rats in the four HE groups. When the rats in the CGL groups had been fed with high energy diet for 8-weeks to 9-weeks, the average weight of rats was significantly lower than that in the HE+H_2O group ($p<0.05$).

Feed Efficiency and Calorie Efficiency

High energy diet was administered for 9-weeks in total. After having been fed with high energy diet for 5-weeks, the rats started receiving sterilized water or supplements for a total of 4-weeks until they had been fed with high energy diet for 9-weeks. Weight gain of each rat was the weight at week-9 minus the weight at week-5, and the total food intake was the summation of food intake from week-6 to week-9. As shown in Table 2, the total weight gain in the HE+H_2O group was significantly higher than that in the control group ($p<0.05$). The total weight gain in the CGL groups were significantly lower than that in the HE+H_2O group. From week-6 to week-9, compared with the control group, the HE+H_2O group had significantly lower total food intake, yet significantly higher total calorie intake. In terms of total food intake and total calorie intake, there was no difference between the CGL groups and the HE+H_2O group. Feed efficiency and calorie efficiency were calculated from the total weight gain, total food intake and total

Table 1. *Effect of Supplements on the Weight of Rats Induced by High Energy Diet*

Weeks	Body Weight (g)				
	Control	HE+H_2O	HE+CGL-L	HE+CGL-M	HE+CGL-H
Week 0	225.1±7.2	226.8±19.7	228.8±5.0	224.3±17.6	225.8±6.8
Week 1	275.8±9.8	294.6±11.1$^{\#\#}$	289.4±14.4	291.3±17.9	293.4±15.1
Week 2	326.8±10.6	351.9±13.4$^{\#\#}$	347.3±15.1	349.9±20.1	351.2±17.9
Week 3	359.8±12.2	406.9±17.7$^{\#\#\#\#}$	405.3±20.5	403.4±23.8	405.1±21.9
Week 4	391.3±9.4	452.5±26.9$^{\#\#\#\#}$	450.3±21.0	450.1±19.3	443.8±31.6
Week 5	412.0±13.5	499.8±30.3$^{\#\#\#\#}$	504.8±29.9	507.5±21.8	498.8±37.4
Week 6	439.7±14.6	534.2±35.5$^{\#\#\#\#}$	521.8±35.0	523.9±22.6	516.3±41.5
Week 7	465.3±17.4	569.2±39.9$^{\#\#\#\#}$	535.3±37.0	531.4±25.1*	524.5±44.3**
Week 8	480.5±19.4	592.3±45.5$^{\#\#\#\#}$	542.8±39.4**	539.6±25.4**	530.6±34.2***
Week 9	495.0±20.1	634.9±42.2$^{\#\#\#\#}$	578.8±41.6**	574.7±24.8**	560.3±53.4***

Control, normal diet group ; HE+H_2O, high energy diet with sterilized water; HE+CGL-L, high energy diet with 296 mg/kg/day of CGL ; HE+CGL-M, high energy diet with 593 mg/kg/day of CGL; HE+CGL-H, high energy diet with 1186 mg/kg/day of CGL. Values were expressed as means±SD, n=12 in each group. Data were analyzed by one-way analysis of variance using the Dunnett's test. $^{\#\#}p<0.01$, $^{\#\#\#\#}p<0.001$ as compared with the control group. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ as compared with the HE+H_2O group.

Table 2. *Effect of Supplements on Feed Efficiency and Calorie Efficiency of Rats Induced by High Energy Diet*

Treatments	Weight Gain (g)	Food Intake (g)	Feed Efficiency (%)	Calorie Intake (Kcal)	Calorie Efficiency (%)
Control	83.0±10.5	810.1±68.1	10.3±1.2	2308.1±193.6	3.6±0.4
HE+H_2O	135.2±14.5$^{\#\#\#}$	614.0±47.2$^{\#\#\#}$	22.0±1.7$^{\#\#\#}$	3216.6±247.6$^{\#\#\#}$	4.2±0.3$^{\#\#\#}$
HE+CGL-L	73.9±17.4***	603.6±21.2	12.2±2.9***	3180.9±110.4	2.3±0.5***
HE+CGL-M	67.2±11.6***	591.4±15.8	11.4±1.9***	3132.9±83.2	2.1±0.4***
HE+CGL-H	61.5±22.1***	580.1±46.6	10.5±3.1***	3106.5±244.7	2.0±0.6***

Control, normal diet group ; HE+H_2O, high energy diet with sterilized water ; HE+CGL-L, high energy diet with 296 mg/kg/day of CGL ; HE+CGL-M, high energy diet with 593 mg/kg/day of CGL; HE+CGL-H, high energy diet with 1186 mg/kg/day of CGL.Values were expressed as means±SD, n=12 in each group. Data were analyzed by one-way analysis of variance using the Dunnett's test. $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ as compared with the control group. $^{***}p<0.001$ as compared with the HE+H_2O group.

Table 3. *Effect of Supplements on Body Fat Amount and Body Fat Percentage of Rats Induced by High Energy Diet*

Treatments	Weight of Adipose Tissue			Body Fat (g)	Body Fat Ratio (%)
	Epididymal Adipose Tissue (g)	Perirenal Adipose Tissue (g)	Mesenteric Adipose Tissue (g)		
Control	6.2±1.1	6.4±1.0	2.9±0.5	15.5±1.9	3.1±0.4
HE+H_2O	16.0±3.7$^{\#\#\#}$	24.1±7.1$^{\#\#\#}$	9.3±3.4$^{\#\#\#}$	49.4±13.8$^{\#\#\#}$	7.7±1.7$^{\#\#\#}$
HE+CGL-L	12.1±2.4*	18.3±5.6*	6.2±2.7**	36.6±9.7***	6.3±1.4*
HE+CGL-M	11.7±2.0**	14.7±2.4***	6.5±1.7*	32.9±5.3***	5.7±0.8**
HE+CGL-H	11.6±3.6**	14.8±5.0***	5.2±1.9***	31.7±9.8***	5.6±1.3***

Control, normal diet group ; HE+H_2O, high energy diet with sterilized water ; HE+CGL-L, high energy diet with 296 mg/kg/day of CGL ; HE+CGL-M, high energy diet with 593 mg/kg/day of CGL; HE+CGL-H, high energy diet with 1186 mg/kg/day of CGL. Body fat defined as the sum of epididymal adipose tissue, perirenal adipose tissue, mesenteric adipose tissue. Body fat ratio (%) defined as (Body fat (g) / Body weight (g))×100.Values were expressed as means±SD, n=12 in each group. Data were analyzed by one-way analysis of variance using the Dunnett's test. $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ as compared with the control group. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ as compared with the HE+H_2O group.

Table 4. *Effect of Supplements on Liver Triglyceride and Cholesterol Concentrations in Rats Induced by High Energy Diet*

Parameters	Control	HE+H_2O	HE+CGL-L	HE+CGL-M	HE+CGL-H
Liver (g)	11.2±0.6	16.4±0.9$^{\#\#\#}$	14.5±1.8**	14.4±1.7**	13.9±2.1***
Liver (%)	2.3±0.1	2.6±0.1$^{\#\#}$	2.5±0.3	2.5±0.3	2.5±0.3
Cholesterol (mg/g tissue)	3.0±0.6	6.1±3.0$^{\#\#}$	5.5±1.5	6.0±2.6	5.9±2.2
Triglyceride (mg/g tissue)	12.4±4.6	44.7±11.5$^{\#\#\#}$	39.0±13.0	37.9±13.5	33.1±10.6*

Control, normal diet group ; HE+H_2O, high energy diet with sterilized water; HE+CGL-L, high energy diet with 296 mg/kg/day of CGL ; HE+CGL-M, high energy diet with 593 mg/kg/day of CGL; HE+CGL-H, high energy diet with 1186 mg/kg/day of CGL.Values were expressed as means±SD, n=12 in each group. Data were analyzed by one-way analysis of variance using the Dunnett's test. $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ as compared with the control group. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ as compared with the HE+H_2O group.

calories from week-5 to week-9. The feed efficiency and calorie efficiency of the HE+H_2O group were significantly higher than those in the control group ($p<0.05$). The feed efficiency and calorie efficiency of the CGL groups were significantly lower than those in the HE+H_2O group.

Changes of Body Fat and Liver Indicators

As shown in Table 3, epididymal, perirenal mesenteric adipose tissue, body fat weight and body fat ratio (%) in the CGL groups were all significantly lower than those in the HE+H_2O group ($p<0.05$). As shown in Table 4, the absolute and relative liver weights, and concentrations of liver cholesterol and liver triglyceride in the HE+H_2O group were all significantly higher than those in the control group; the absolute liver weight in the three CGL groups were significantly lower than that in the HE+H_2O group ($p<0.05$), but there was no significant difference in the relative liver weight and the concentration of liver cholesterol; the concentration of liver triglyceride in the HE+CGL-H group was lower than that in the HE+H_2O group ($p<0.05$).

Serum Biochemical Test

As shown in Table 5, among the 13 biochemical indicators tested in serum, the concentrations of triglyceride, free fatty acid, ketone body and glucose in the HE+H_2O group were significantly higher than those in the control group, and the remaining 9 indicators did not differ significantly. All three doses of the CGL groups were able to reduce the triglyceride concentration in serum; HE+CGL-M and HE+CGL-H reduced the free fatty acid, ketone body and glucose concentrations in serum, but they had no significant effect on the other 9 indicators, no abnormal was observed.

Table 5. *Effect of Supplements on Plasma Biochemical Properties of Rats Induced by High Energy Diet*

Parameters	Control	HE+H_2O	HE+CGL-L	HE+CGL-M	HE+CGL-H
AST(U/L)	153.3±16.6	172.2±28.4	190.1±32.9	176.9±20.7	165.2±44.7
ALT(U/L)	48.9±7.8	48.7±11.9	51.8±16.2	45.5±5.9	47.7±9.2
TG (mg/dL)	36.3±11.1	47.4±6.1$^{\#}$	39.8±5.6	39.0±9.0	36.9±11.2*
TC (mg/dL)	61.0±11.2	69.4±16.3	63.5±16.8	58.1±13.8	60.9±13.5
LDL-C (mg/dL)	40.1±9.3	37.9±11.4	37.4±13.3	36.6±11.6	39.0±11.2
HDL-C (mg/dL)	18.6±5.1	23.0±9.8	23.4±3.3	18.3±3.4	21.1±4.9
FFA (mmol/L)	0.85±0.09	1.01±0.09$^{\#}$	0.93±0.26	0.80±0.16**	0.78±0.11**
KB (nmol/L)	199.9±49.5	362.8±65.6$^{\#\#\#}$	313.6±82.4	294.3±60.2	267.1±94.4**
Crea (mg/dL)	0.48±0.21	0.46±0.10	0.44±0.21	0.42±0.14	0.50±0.27
UA (mg/dL)	1.54±0.35	1.82±0.30	1.60±0.32	1.55±0.22	1.80±0.42
Na (mEq/L)	144.0±0.9	144.8±1.0	144.8±0.8	144.3±0.9	144.1±1.0
K (mEq/L)	4.7±0.4	4.7±0.6	4.4±0.4	4.6±0.1	4.7±0.3
Glu (mg/dL)	112.1±23.8	153.8±17.3$^{\#\#\#}$	138.0±19.6	112.6±10.3***	129.3±29.4*

Control, normal diet group ; HE+H_2O, high energy diet with sterilized water ; HE+CGL-L, high energy diet with 296 mg/kg/day of CGL; HE+CGL-M, high energy diet with 593 mg/kg/day of CGL; HE+CGL-H, high energy diet with 1186 mg/kg/day of CGL.Values were expressed as means±SD, n=12 in each group. Data were analyzed by one-way analysis of variance using the Dunnett's test. $^{\#}p<0.05$, $^{\#\#\#}p<0.001$ as compared with the control group. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ as compared with the HE+H_2O group.AST, aspartate aminotransferase;ALT, alanine aminotransferase;TG, triglyceride;TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; FFA, free fatty acid; KB, ketone body; Crea, creatinine; UA, uric acid; Na, sodium; K, potassium; Glu, glucose.

DISCUSSION

Feeding one, two and four-fold the doses recommended for humans had a significant inhibitory effect on the weight, feed efficiency, calorie efficiency, body fat amount and body fat ratio of the rats increased by high energy diet. The initial weight of Sprague Dawley® male rats used in this study was approximately 225 g, and they were fed with high energy diet (5.24 Kcal/g) for 9-weeks. The results in Tables 1 and 3 show that compared with the control group the HE+H_2O group had 28.2% higher body weight, and 218% higher body fat (epididymal, perirenal, mesenteric adipose tissues). High energy diet significantly increased the accumulation of body fat in the rats. After being fed with high energy diet for 5 weeks, CGL supplements were administered daily for 4-weeks. Calculation was made on the basis of the data of those having been fed with high energy diet for 9-weeks. HE+CGL-L reduced body weight by 8.8% and body fat by 25.7%; HE+CGL- M reduced body weight by 9.4% and body fat by 33.2%; and HE+CGL-L reduced body weight by 11.8% and body fat by 35.9%. These results show that the CGL significantly reduced body fat accumulation in the rats.

Feed efficiency refers to the degree of digestion, absorption, and utilization of food after being ingested. The higher the percentage, the more fully the food can be utilized by the body. During the period of administering CGL supplements, feed efficiency and calorie efficiency can be calculated from the total weight gain, total feed intake and total calorie intake from week-5 to week-8. The feed efficiency and calorie efficiency of the CGL groups were significantly lower than those in the HE+H_2O group. These results show that the CGL reduced body weight and body fat accumulation by lowering feed efficiency and calorie efficiency. The caloric intake converted from feed intake gave the same results, that is, the calorie efficiency of CGL groups were significantly lower than that of the HE+H_2O group. In the safety test of 13 items in blood plasma, the CGL reduced the concentrations of free fatty acid, triglyceride, ketone body and glucose, but had no effect on the other 9 parameters, including AST, indicating that liver and kidney function indices were unaffected. As there is higher oil and fat content in high energy diet, besides the increase in blood free fatty acid and triglyceride concentrations, the concentrations of liver triglycerides and cholesterol in the rats also increased significantly; HE+CGL-H was able to significantly improve the concentration of liver triglycerides.

Previous study found that feeding mice with a high-fat diet and containing 0.5% (w/w) catechins helps to inhibit obesity caused by high-fat diet. After 12-weeks of feeding, the mice's weight can be significantly decreased. Tea catechins may prevent or improve obesity by modulating lipid metabolism.[16] The report of the meta-analysis on green tea and weight loss shows that taking catechins for 12-weeks on average could reduce the mean weight of the treatment subjects by 1.31 kg.[17] Daily intake of 270 to 1200 mg of catechin products could clearly affect human weight and cause physical changes. The possible mechanisms of catechins in green tea to help weight loss include energy consumption, changes in lipid metabolism, appetite suppression, and reduction in the absorption of glucose, probably by inhibiting the activities of α-amylase and α-glucosidase to reduce nutrient absorption.[8] Based on another meta-analysis on the results of 15 studies, compared with decaffeinated catechin, the combination of catechin and caffeine was able to significantly reduce the weight by 0.44 kg, BMI and waist circumference.[18] Supplements used in this study contain 80 to 120 mg of catechin per tablet, and the green tea extract contains approximately 0.7% caffeine. Taking 4 tablets per day would result in a dose of 320 to 480 mg catechin, which is consistent with the trend in the literature on the meta-analysis.

The lotus leaf extract used in this study contains 2% nuciferine and 5% flavonoids. In the *in vitro* tests, lotus leaf ex-

tract had a stronger inhibiting effect on lipase than on α-amylase. After phenolic compounds were eliminated from the lotus leaf extract, the inhibitory activity on lipase and α-amylase also disappeared.[12] The inhibiting effect on enzymes is known to lower the carbohydrate digestion rate, reduce the digestion and absorption of glucose, and help ameliorate postprandial hyperglycemia, thus preventing glucose from being transported to fat tissues, as well as suppressing the synthesis and accumulation of triglyceride.[19] In a study, it was pointed out that epigallocatechin (EGC), which is rich in lotus seedpod extract (LSE), has a hepatoprotective effect. It uses oleic acid to induce Hepa G2 cells to conduct experiments. By measuring oxidative stress and apoptosis pathways, it is confirmed that LSE has the effect of reducing lipid accumulation and lipid toxicity.[20] In addition, the part of nuciferine also has the effect of improving lipid metabolism and anti-oxidation. Studies have shown that *in vitro* experiments, using oleic acid to induce Hepa G2 cells for experiments, nuciferine can reduce triglyceride accumulation and effectively reduce fatty acid content.[21] Previous study indicated that nuciferine can reduce the weight gain and fat accumulation of high fat diet-fed rats, affect the intestinal microbial composition, increase short-chain fatty acids. The anti-obesity effect may be related to the composition of the intestinal flora and the regulation of potential functions.[22] It was also observed in this study that the supplement containing nuciferine tended to lower total triglyceride concentration in liver, and all three doses of the supplements could significantly reduce serum total triglyceride concentration ($p<0.05$).

Previous study have pointed out that feeding rats with a high-fat diet and then giving 250 mg/kg L-carnitine, the results show that the rats' blood lipids can be normalized, and decrease serum triglycerides, cholesterol, and peripheral adipose tissue.[23] On the other hand, it has also been observed that L-carnitine can change the lipid metabolism of high fat diet-fed rats with inhibition of stearoyl-CoA desaturase-1 (SCD-1) activity inducing an increase in fatty acid oxidation and a decrease in body fat.[24] When obese women aged 20 to 40-years-old took 1000 mg of L-carnitine daily for 12-weeks, its effect was better than raspberry ketone; the former could significantly improve cholesterol, triglyceride, low density lipoprotein (LDL) and high density lipoprotein (HDL).[25] The supplements used in this study contain 300 mg of L-carnitine per tablet; if an adult takes 4 tablets daily, he or she will be getting 1200 mg of L-carnitine, and the long-term use is expected to reduce obesity-related parameters.

LIMITATION

Although the results of animal experiments are remarkable, the effects and variation in humans are still unknown. The prevention and maintenance of obesity after weight loss is still to be discussed.

CONCLUSION

CGL supplements can significantly reduce the weight, body fat (epididymal, perirenal, mesenteric adipose tissue), body fat ratio, feed efficiency and calorie efficiency of the rats. These results clearly show that CGL can alleviate fat accumulation in rats induced by high energy diet. In conclusion, the results of the animal experiments clearly show that the fat accumulation and high body fat percentage induced by high energy diet can be significantly reduced in rats by using supplement of the same dose recommended for humans. It has the potential as a new dietary supplement for weight loss. Therefore, human experiments should be tested and thorough the study of the effects in the future, investigate how to achieve the maintenance of human body effects and the improvement of variables.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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