Original Article

Efficacy of *Pistacia lentiscus* Plant (Rumi Mastagi) in Comparison to Levosulpiride in Patients with Diabetic Gastroparesis: A Double-Blind Non-Inferior Randomised Control Trial Study

Ajaypal Singh, Ravi Kant, Rohit Raina, Vandana Dhingra[1], Rajeev Nema[2], Mukesh Chand Bairwa, Varsha Kanwar[3], Rifika I Sukhes Mukherjee[4], Anissa Atif Mirza[5], Mayank Agarwal

Departments of Internal Medicines and [1]Nuclear Medicine, All India Institute of Medical Sciences, Veerbhadra Road, Rishikesh, Uttarakhand, [2]Department of Biosciences, Manipal University, Jaipur, [3]Department of Pathology, Jawahar Lal Nehru Medical College, Ajmer, Rajasthan, [4]Department of Biochemistry, All India Institute of Medical Sciences, Bhopal, Madhaya Pradesh, [5]Department of Biochemistry, All India Institute of Medical Sciences, Veerbhadra Road, Rishikesh, Uttarakhand, India

Abstract

Introduction: Gastrointestinal neuropathies are frequently found in diabetic patients. The pathogenesis of diabetic gastroparesis (DG) is multifactorial. The usual treatment for DG includes dietary modifications, prokinetic and antiemetic agents. There is increasing demand for more effective medicines to treat DG. The current study was conducted on the *Pistacia lentiscus* stem extract to add to the armamentarium of DG treatment and to find the efficacy of *P. lentiscus* plant extract (mastic gum) in comparison to levosulpiride in DG for improvement in gastroparesis symptoms and gastric emptying scintigraphy (GES) in a single centric double-blind non-inferiority randomised control trial. **Methods:** Thirty-eight individuals were recruited and equally randomised into two study groups based on Gastroparesis Cardinal Symptom Index (GCSI) score and TC_{99} Radionuclide GES, mastic gum group and levosulpiride group. Both pre and post-intervention (8 weeks) GCSI scores were calculated, GES was performed to quantify the improvement in gastric emptying. Power analysis was performed using G*POWER software version 3.1.9.7 and data analysis using SPSS 23.0, variables measured in mean ± standard deviation (SD). Various statistical tests were used such as independent t-test, Chi-square test or Fisher's exact test, Wilcox Mann–Whitney test, analysis of variance (ANOVA) test, and posthoc pairwise tests. **Results:** The mastic gum is found effective in the improvement of 4 h gastric emptying percentage from the mean (SD) 76.60 (± 9.96) to mean (SD) 97.20 (2.17)% ($P < 0.001$). Mastic gum has the property of HbA1c reduction, which is more significant than that of levosulpiride ($P = 0.044$). Mastic gum also had significant Low density lipoprotein (LDL) (mg/dL) levels reduction, ($P < 0.001$), compared to levosupiride. An absolute increase was observed in haemoglobin (HB) level in mastic gum at a 2-month mean (SD) of 1.03 (0.77) (g/dL) (*P*-value <0.001). **Conclusions:** To our knowledge, this is the first study to compare the effect of levosulpiride with mastic gum concerning improvement in diabetic gastroparesis (DG) using GES. In the study, mastic gum was found to have great properties to improve DG with many important pleiotropic effects.

Keywords: Chios mastic gum (CMG), diabetic gastroparesis (DG), gastric emptying (GE), gastrointestinal cardinal symptom index score (GCSI), HOMA IR, inflammatory bowel disease (IBD), radionuclide gastric emptying scintigraphy (GES), the half-maximum inhibitory concentration IC (50) non-alcoholic fatty liver disease (NAFLD)

Introduction

Diabetes is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.[1] Gastrointestinal neuropathies in patients with diabetes represent vital aspects of the chronic course of the disease.[2] The main pathogenic mechanisms of both upper and

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_84_23

Address for correspondence: Dr. Ravi Kant, Department of Internal Medicines, All India Institute of Medical Sciences, A-Block, Veerbhadra Road, Rishikesh, Uttarakhand, India. E-mail: drkantr2006@gmail.com

Submitted: 23-Feb-2023 **Revised:** 19-Apr-2023
Accepted: 22-Apr-2023 **Published:** 26-Feb-2024

How to cite this article: Singh A, Kant R, Raina R, Dhingra V, Nema R, Bairwa MC, *et al*. Efficacy of *Pistacia lentiscus* plant (rumi mastagi) in comparison to levosulpiride in patients with diabetic gastroparesis: A double-blind non-inferior randomised control trial study. Indian J Endocr Metab 2024;28:35-42.

lower gastrointestinal (GI) dysfunctions include abnormalities of motor function, visceral hypersensitivity, inflammatory state, abnormal secretion of GI hormones, autonomic dysfunction and genetic predisposition.[3] This can be perceived as chronic delayed gastric emptying associated with nausea, vomiting, postprandial fullness, weight loss, anorexia and abdominal pain without evidence of mechanical obstruction.[4] The prevalence of diabetic gastroparesis (DG) is higher in patients with type 1 diabetes mellitus (T1DM) compared to type 2 diabetes mellitus (T2DM). Prevalence in T1DM was found to be 4.8% up to 64%.[4] At present, the treatment available for DG is symptomatic only, for example, dietary modifications, antiemetic agents and prokinetic agents.[4,5] In refractory cases, patients may need high-cost invasive procedures, for example, surgeries and gastric electrical stimulation.[6] Because of this, there is a need to find a drug, which can help to improve gastroparesis symptoms with sustainable effects. This study was conducted to find a naturally occurring medicinal plant that has therapeutic potential to treat gastroparesis with minimal adverse effects. Many foreign studies and randomised controlled trials have shown that *Pistacia* species plant (cashew family) extracts are widely used in many gastrointestinal diseases and DG with great results.[7-13] Mastic gum was found to be highly effective in a human randomised trial on patients with non–alcoholic fatty liver disease (NAFLD) over a 6-month duration. Authors claimed that mastic gum significantly improved the gut microbiota dysbiosis and lipid metabolism and liver fibrosis in NAFLD patients.[12] It is also used in inflammatory bowel disease (IBD) patients as anti-TNF-alpha inhibitory agent and helps in the regulation of Th 17 cells and is found to be effective in IBD patients.[12] Its anticancer action has also been proven in various *in vivo* and *in vitro* studies, the various cytokines present in mastic gum are responsible for its anticancer properties. Inhibition of RAS–Rho signaling, NF κB (nuclear factor kappa B) and JAK STAT pathways, anti VEGF (vascular endothelial growth factors) prevent reduced glutathione depletion, that appears to be potential therapeutic targets for its phytochemicals.[13] Given trial was a novel study in the Indian set-up as there is no Indian study to support the evidence although many species of *Pistachio* plants are present in the Great Himalayan region.[14]

Materials and Methods

It was a double-blind randomised noninferiority controlled trial. The study was conducted with the standards as per the Helsinki Declaration of 1975, as revised in 2000. In total, 867 patients were screened based on the GCSI score in diabetic outpatient department (OPD), after exclusion criteria, 39 patients were enrolled in the study who all were having delayed gastric emptying on GES. Informed consent was taken from all study participants and written statement in form of consent was obtained. After physical and chemical characterisation of mastic gum, it was found that it has a green and rustic odour (Naves, 1974); soluble in isopropyl alcohol, acetone, hexane, methanol, chloroform, diethyl ether and n-butyl ether; insoluble in water (1%) (hydrophobic); moisture-max. 1.5%; total ash-0.2%; melting point 94–98°C; acid value-115–121; stable under normal conditions of use and no hazardous decomposition. A novel micronisation technology and hydrophilic polymer (HPMC, MCC) makes the hydrophobic mastic gum into a hydrophilic compound, increasing its bioavailability and sustained release with less variability and better therapeutic outcomes. These properties of oral pure vegan capsules make it a novel preparation. Computer-generated randomisation was performed to divide into two different groups, Group A received mastic gum and Group B received levosulpiride. One patient was lost to follow-up. Finally, 19 patients in each group were analysed for results. After a thorough phytochemical analysis, the mastic gum capsules, containing 500 mg of gum and identical capsules of levospupiride 25 mg, were formulated after due approval from competent authorities. Inclusion criteria-both type 1, type 2 diabetes mellitus patients with age more than 18 years and diagnosed with DG based on GCSI score and GES. Exclusion criteria-non-diabetic patients, patients with age <18 years of age, peptic ulcer disease (PUD), irritable bowel syndrome, any known or clinically suspected organic GI mechanical obstruction or systemic diseases, history of any gastric surgery or gastric bypass, vagotomy, end-organ failure, diabetes in pregnancy, any psychiatric disorder, using drugs interfering with GI motility, for example, domperidone and metoclopramide. The above diseases were ruled out by appropriate clinical assessment and patient case sheet records. Group A patients received the capsule mastic gum at a dose of 500 mg per oral twice daily and Group B patients received capsule levosulpiride 25 mg per oral twice daily. No antidiabetic medicines were held for patients. Pre-intervention baseline GES, fasting plasma glucose (FPG) levels,postprandial plasma glucose levels (PPPG), HbA1c (Glycated haemoglobin) (%), lipid profile and routine blood parameters were noted. Patients were regularly followed telephonically for any adverse drug reaction. After 8 weeks post-intervention, the same parameters were compared and analysed. Data were analysed using SPSS 23.0 and variables were measured as mean ± SD. Various statistical tests were used such as independent *t*-test, Chi-square test or Fisher's exact test, Wilcox–Mann–Whitney test, ANOVA test, posthoc pairwise tests, and Wilcoxon signed-rank test. Two groups were compared by the generalised estimating equations method.

Ethical aspects

After the Institutional Ethics Committee (ECR/736/ Inst/ UK/2015/RR-21) approval (No. 392/IEC/PGM/2021), and CTRI Registration no. CTRI/2022/03/041419, the study was conducted with the standards as per the Helsinki Declaration of 1975, as revised in 2000.

Results

The baseline characteristics of all enrolled patients were analysed and reported [Table 1]. The mean age in Group A was (mean ± SD) 52.95 ± (14.19) years and in Group B was

Table 1: Detailed baseline characteristics of the study population at the pre-intervention timepoint

Parameters (pre-intervention)	Group		*P*
	A (*n*=20) Mean±SD	B (*n*=19) Mean±SD	
Age (years)	52.95±14.19	52.21±11.92	0.861[1]
Gender			0.429[3]
Male	12 (60.0%)	9 (47.4%)	
Female	8 (40.0%)	10 (52.6%)	
Total duration of DM (years)	12.45±8.03	9.63±4.41	0.182[1]
BMI (Kg/m^2)***	23.10±3.97	25.62±3.03	0.046[4]
T2DM	18 (90.0%)	18 (94.7%)	1.000[2]
GCSI score	35.30±4.88	34.89±4.12	0.622[4]
T1DM	2 (10.0%)	1 (5.3%)	1.000[2]
HTN	3 (15.0%)	5 (26.3%)	0.451[2]
Hypothyroidism	1 (5.0%)	2 (10.5%)	0.605[2]
Dyslipidaemia	1 (5.0%)	3 (15.8%)	0.342[2]
4-h Emptying (%)	76.60±9.96	72.53±9.66	0.203[1]
$T^{1/2}$ (min)	163.80±36.75	165.76±31.67	0.859[1]
$T^{1/2}$ (min)	163.80±36.75	165.76±31.67	0.859[1]
FBS (mg/dL)	155.30±23.60	160.26±32.80	0.822[4]
Postprandial Glucose (mg/dL)	204.05±39.70	191.22±40.81	0.473[4]
Hb1Ac (%)	8.64±1.10	8.62±0.84	0.926[1]
Triglycerides (mg/dL)	190.35±44.21	202.89±47.70	0.401[1]
Total cholesterol (mg/dL)	231.60±39.31	219.28±49.04	0.402[1]
LDL (mg/dL)	149.90±35.83	127.72±33.00	0.055[1]
S. creatinine (mg/dL)	2.22±5.43	0.62±0.40	0.092[4]
Total bilirubin (mg/dL)	0.56±0.35	0.59±0.50	0.910[4]
Haemoglobin (g/dL)	12.24±1.46	12.37±2.00	0.822[4]
TLC (/mm≥)	6285.45±1821.47	5791.21±1630.23	0.377[1]

***Significant at $P<0.05$, 1: *t*-test, 2: Fisher's exact test, 3: Chi-squared test, 4: Wilcoxon–MannWhitney *U* test

mean ± (SD) 52.21 ± (11.9) years. It was found that patients with the age between 41 years and 60 years had a higher risk of developing gastroparesis symptoms and delayed gastric emptying over various age groups. The total number of male patients with delayed gastric emptying was more than the number of females with delayed gastric emptying, 58 (59.8%) and 39 (40.2%), respectively. Both pre-intervention groups were matched with the duration of diabetes, with no statistically significant difference between the two groups, the *P* value was 0.861*, t-test = 1.367*, *Point-Biserial Correlation 0.22 (small effect size)*. There was no correlation between the age of patients with abnormal gastric emptying and normal gastric emptying, for example, age (years) mean (SD) 52.59 ± (12.97) and 49.10 ± (11.65) ($P = 0.180$) (*t-test*), respectively. The total duration of diabetes was also not statistically different in patients with abnormal gastric emptying and normal gastric emptying, for example, 11.08 ± (6.59) and 8.84 ± (5.28) ($P = 0.086$) (Wilcoxon–MannWhitney *U* test), respectively, although it was higher in patients with delayed GES. There was no significant correlation in body mass index (BMI) (Kg/m^2) of patients with delayed emptying vs. normal gastric emptying, with mean ± (SD) 24.33 ± (3.72) and 24.98 ± (3.06), respectively ($P = 0.367$) (*t*-test). Patients were regularly followed on Out patient department (OPD) visits or telephonic communication; after the 8 weeks post-intervention, both groups were re-investigated for all baseline investigation and intra-group and inter-group comparisons were performed with various statistical tests [Table 2].

There was a significant improvement in 4-h gastric emptying percentage in both groups (intergroup comparison, *P* value = 0.249) [Figure 1]. There was a statistically significant reduction in mean $T^{1/2}$ (min) on GES in both groups. Group A was having more reduction in T1/2 (min), in comparison to group B [Figure 2]. Post-intervention analysis of lipid profile is suggestive of a significant reduction in total cholesterol levels and Low density lipoprotein (LDL) cholesterol levels in pre-intervention matched groups [Table 3, Figure 3]. Post-intervention data were suggestive of a statistically significant increase in haemoglobin (gm/dL) levels in Group A than Group B. A few adverse drug effects were noted with group B patients, for example, loose stools, increased sleepiness, generalised fatigue and low energy, one patient in group A had mild gastritis symptoms in the 1st week of therapy as reported by patients.

Discussion

Pistacia plant extracts are widely accepted as a part of complementary and alternative medicine (CAM) in various

European medicinal uses. Given trial is a novel study in an Indian setup. Mastic gum is not only a natural product with minimum or no side effects but also easily acceptable for the majority of geriatric as well as younger diabetic population, and has excellent taste and aroma of terpenes.[15] The Ayurveda Pharmacopoeia of India (1999) also contains a monograph referring to the resin of *P. lentiscus* L. called as 'Rumi mastagi' and mentioned its characteristics.[16] In our trial, we observed that the total number of male patients with abnormal (delayed) gastric emptying was higher than the total number of female patients, that is, 53.8% and 46.2%, respectively. This indicates that probably, the prevalence of gastroparesis based on GCSI score or delayed gastric emptying is higher in males than females in the North Indian population although the total number screened was also less in the study. Various studies claimed a higher percentage of gastroparesis in female diabetic patients.[17-20] The mean duration of diabetes in patients with delayed gastric emptying is higher than that with normal GES, that is, 11.08 ± 6.59 and 8.84 ± 5.28, respectively, but statistically non-significant (*P*-value = 0.086), which indicated that patients having longer duration of diabetes were associated with an increased risk of DG. It indicates there is no association between BMI and delayed gastric emptying (*P = 0.367)*. Although it was found that patients with high BMI had higher chances of development of gastroparesis symptoms. Out of total gastroparesis patients based on GCSI score (97), 52 (53.60%) patients had BMI more than 25 Kg/m². In previous studies, obesity is also mentioned as an independent predictor of any cardinal manifestation of gastroparesis (odds ratio = 9.86, 95% confidence interval = 1.4–69.2, *P* = 0.02).[21] Post intervention, 4 h emptying (%) was measured and changes compared between two groups; no statistically significant difference was found between the two groups (*P* = 0.255). The overall mean change in $T^{-1/2}$ (mins) values showed no

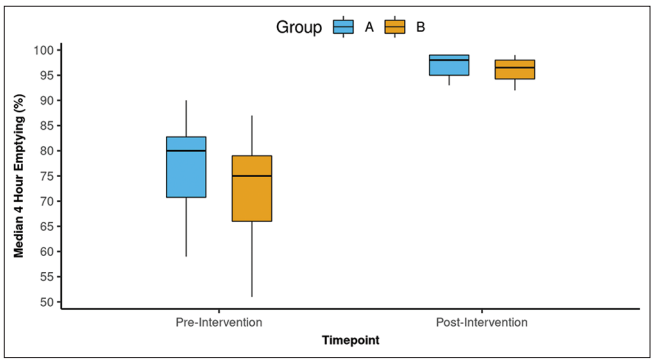

Figure 1: Box-and-Whisker plot below depicts the distribution of 4-h emptying (%) over different time points. In each box, the middle horizontal line represents the median 4 h emptying (%), upper and lower bounds of the box represent the 75th and the 25th centiles of 4-h emptying (%) respectively, and the upper and lower extents of the whiskers represent the Tukey limits for 4-h emptying (%) at each of the time points

Table 2: Detailed characteristics and their changes at the post-intervention time point in the study population

Parameters (post-intervention)	Group		*P*
	A (*n*=19)	B (*n*=19)	
	Mean±SD	Mean±SD	
4-h emptying (%)	97.20±2.17	96.39±2.28	0.213[4]
Change in 4-h emptying (%)	20.60±9.27	24.17±9.47	0.249[1]
$T^{1/2}$ (min)	85.46±20.00	95.76±11.83	0.082[4]
Absolute change in $T^{1/2}$ (min)	-78.33±28.44	-71.53±29.23	0.473[1]
FPG (mg/dL)	127.60±14.34	132.83±15.84	0.295[1]
Absolute change in FBS (mg/dL)	-27.70±20.40	-25.50±23.46	0.761[1]
PPPG (mg/dL)	162.15±21.33	160.83±16.42	0.861[4]
Absolute change in PPBS (mg/dL)	-41.90±32.81	-30.39±29.59	0.279[4]
HbA1c (%)	7.52±0.55	7.57±0.27	0.734[1]
Absolute change in HbA1c (%)	-1.12±0.71	-0.95±0.64	0.629[4]
Triglycerides (mg/dL)	163.20±30.60	179.67±20.14	0.056[1]
Absolute change in triglycerides (mg/dL)	-27.15±29.19	-17.28±34.53	0.169[4]
LDL (mg/dL)	123.35±27.67	126.44±22.77	0.708[1]
Absolute change in LDL (mg/dL)***	-26.55±14.39	-1.28±23.92	0.002[4]
Total cholesterol (mg/dL)***	173.55±33.00	201.33±36.90	0.030[4]
Absolute change in total cholesterol (mg/dL) ***	-58.05±32.08	-17.94±36.43	0.001[1]
S. creatinine (mg/dL)	0.78±0.70	0.48±0.21	0.260[4]
Absolute change in s. creatinine (mg/dL)	-1.44±5.50	-0.07±0.28	0.306[4]
ALP (U/L) ***	100.00±15.67	88.44±14.98	0.026[1]
Haemoglobin (g/dL)	13.28±1.37	12.54±1.59	0.137[1]
Absolute change in haemoglobin (g/dL) ***	1.03±0.77	0.17±0.89	0.007[4]
GCSI score	16.35±2.28	15.94±2.04	0.564[4]
Change in GCSI score	-18.95±4.06	-18.94±4.04	0.997[1]

***Significant at *P*<0.05, 1: *t*-test, 2: Fisher's exact test, 3: Chi-squared test, 4: Wilcoxon–Mann–Whitney *U* Test

Table 3: Summary of the absolute mean change in total cholesterol (mg/dL) from the pre-intervention time point to the various follow-up time points. It also summarises the statistical comparison of the two groups in terms of this difference. Intergroup comparison *P*=0.003

Timepoint comparison	Change in total cholesterol (mg/dL) from pre-intervention to follow-up time points				*P*
	Group: A		Group: B		
	Mean (SD) of absolute change	*P*	Mean (SD) of absolute change	*P*	
1 Month-post-intervention	-35.50 (16.53)	0.003	-21.94 (21.75)	0.026	0.041
2 Months-post-intervention	-58.05 (32.08)	<0.001	-17.94 (36.43)	0.396	0.003

Post-hoc pairwise tests for the Friedman test performed using the Nemenyi test were used to explore the statistical significance of the change in total cholesterol (mg/dL) from the pre-intervention time point to the various follow-up time points. Group comparisons for change in total cholesterol (mg/dL) were performed using Wilcoxon–Mann–Whitney test. The green background denotes a statistically significant difference at $P<0.05$

Table 4: Summary of the mean (SD) percent change in haemoglobin (g/dL) from the pre-intervention time point to the various follow-up time points. It also summarises the statistical comparison of the two groups in terms of this difference

Timepoint comparison	Percent change in haemoglobin (g/dL) from pre-intervention to follow-up time points				*P*
	Group: A		Group: B		
	Mean (SD) % change	*P*	Mean (SD) of % change	*P*	
1 Month-post-intervention	1.5% (4.8)	0.254	3.5% (3.4)	0.032	0.140
2 Month-post-intervention	8.8% (7.1)	<0.001	2.2% (8.3)	0.913	0.017

Post-hoc pairwise tests for the Friedman test performed using the Nemenyi test were used to explore the statistical significance of the change in haemoglobin (g/dL) from the pre-intervention time point to the various follow-up time points. Group comparisons for change in haemoglobin (g/dL) were performed using Wilcoxon–Mann–Whitney test. The green background denotes a statistically significant difference at $P<0.05$

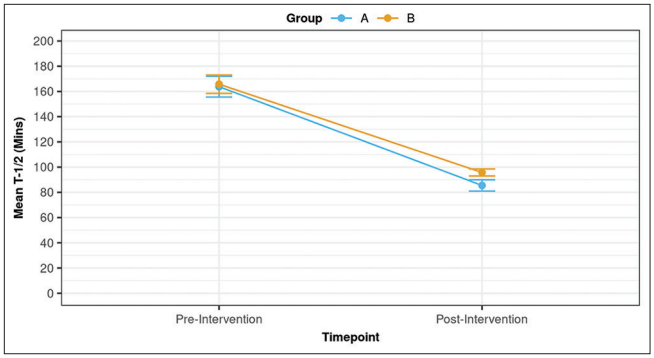

Figure 2: The line graph depicting the change in $T^{1/2}$ (mins) over time in the two groups. Group A was having more reduction in $T^{1/2}$ (min), in comparison to Group B

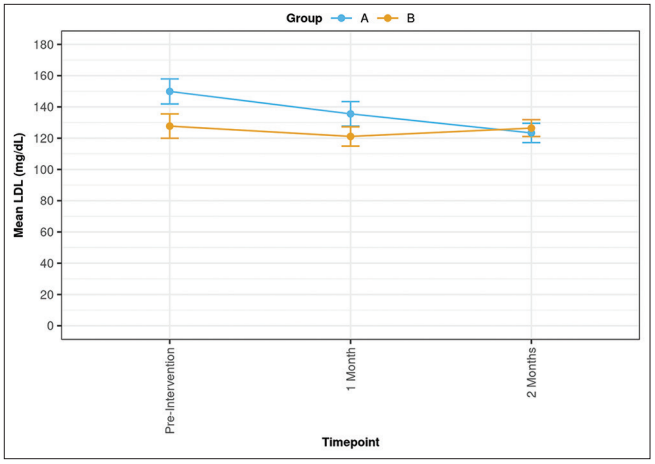

Figure 3: Graphs depict the change in LDL (mg/dL) over time in the two groups at various time points, suggesting a more and persistent fall in LDL levels in Group A in comparison to Group B. Within the group A, changes were statistically significant reduction (*P*-value, Friedman's test <0.001)

statistically significant difference between the two groups post intervention ($P = 0.395$); however, absolute value of reduction was more in group A (Wilcoxon test: V = 210.0, $P \leq 0.001$). Changes in 4 h emptying (%) and T½ time of gastric emptying (GE) on scintigraphy can be interpreted by the role of alpha and beta terpenes, pinene, and limonene present in *Pistacia* species plants. These components may increase peristaltic contraction in the fundus and antrum with the strengthening of the gastric smooth muscles and nerves, which in turn causes improvement in delayed gastric symptoms.[22,23] Plasma glucose levels, HbA1c (%) levels were measured at pre-intervention, at points of time 1 month, 2 months, and compared with group-matched patients. The total number of patients taking insulin therapy were three in Group A, four in Group B, and no patient was newly started on insulin therapy.

In Group A, there was a significant absolute reduction in the mean HbA1c (%) at 2 months ($P = 0.044$) compared to group B ($P = 0.106$). This reduction in HbA1c (%) can be interpreted as an improvement of gastroparesis symptoms having the main effect on carbohydrate absorption through the release of gut peptides and enhanced absorption of oral hypoglycaemic drugs.[7,24-26] Improvement in glycaemic control can be explained by a better synchronisation between the onset of action of exogenous insulin and the increase in GI motility, which leads to the release of nutrients from the stomach into the intestine and absorption into the general circulation.[27] For

patients with diabetes who are being treated with pre-prandial regular insulin injections, delayed gastric emptying may cause hypoglycaemia 2–3 h after a meal (when the absorption of food is not yet completed). In contrast, hyperglycaemia may occur 4 h or more after a meal when the action of regular insulin decreases.[27] Percent change in mean FPG (mg/dL) was statistically significant in Group A-16.5% (11.6) (reduction) at the 2-month time point ($P < 0.001$). This effect of reduction in blood sugar levels could be due to triterpenes and oleanolic acid (OA) in mastic gum.[14] It has a beneficial effect on pancreatic beta cells, that is, promoting insulin action by increasing insulin secretion and inhibiting protein tyrosine phosphatase-1B.[28] OA increases insulin biosynthesis and secretion and improves glucose tolerance. It also promotes β-cell survival and proliferation by multiple mechanisms, for example, *a*) acetylcholine release and activation of M3 muscarinic receptors, *b*) enhancement of the glucagon-like peptide-1 (GLP)-1 release by agonist action on the TGR-5 receptors, *c*) alleviation of oxidative stress, *d*) stimulation of the Src-homology phosphotyrosine phosphatase two activities and PKB/Akt pathway- protein kinase B Akt pathway pathway and *e*) improvement of the β-cell survival and proliferation.[28] [Figure 4]. In the study reduction in postprandial plasma glucose levels (PPPG) was higher in group A. An *in vitro* study demonstrated that CMG has the property of dose dependent, dual inhibition of alpha glucosidase and alpha amylase mediated enzymatic starch digestion bioassay, with half maximum inhibitory concentration IC (50) s; 46.98, compared to acarbose IC50 1.2 µg/IL. Comparable *in vivo* results were obtained for starch-fed rats, suggestive of anti-diabetic properties of mastic gum plant extracts.[29] Serum LDL level (mg/dL) was statistically significantly reduced in group A compared to group B, and the mean change in LDL (mg/dL) over time was compared in the two groups using the generalized estimating equations method ($P \leq 0.001$). Absolute total cholesterol levels (mg/dL) reduced statistically significantly in group A mean (SD-58.05 (32.08) compared to group B mean (SD)-17.94 (36.43) ($P = 0.003$) at a post-intervention time point, calculated by the generalized estimating equations method. No significant change was noticed in triglyceride levels in the study. In a study, mastic gum is claimed to have a significant improvement in lipid profile and insulin resistance (HOMA-IR, $P = 0.009$) and insulin levels in the study population after 6 months of use.[30] The safety of various organs such as renal and liver has been ensured in various studies.[30,31] In a previous prospective, randomised, placebo-controlled pilot study over 179 volunteers, it is stated that the individuals who received a daily total dose of 1 g of crude CMG had a reduction in total cholesterol by 11.5 mg/dL ($P < 0.05$) and FPG by 4.5 mg/dL ($P < 0.05$). As stated in our study as well, no effects were noticed in total triglyceride levels as mentioned by Kartalis *et al.*[31] Research suggests that effects of various phytochemical of CMG such as Oleanolic acid (OA), gallic acid on lipid metabolism preferably by the activation of peroxisome proliferator activated receptors (PPARs) and restoration of GSH levels and downregulation of CD36 expression, even at the mRNA level.[14,32-34] In the post-intervention analysis, a significant improvement in haemoglobin levels was seen in the study group who received mastic gum. Post-hoc pairwise tests for Friedman's test performed using Nemenyi test were used to measure the percentage increase in Group A (8.8%, 7.1) and Group B (2.2%, 8.3) (P = 0.017). This is suggestive of probable hematinic effect

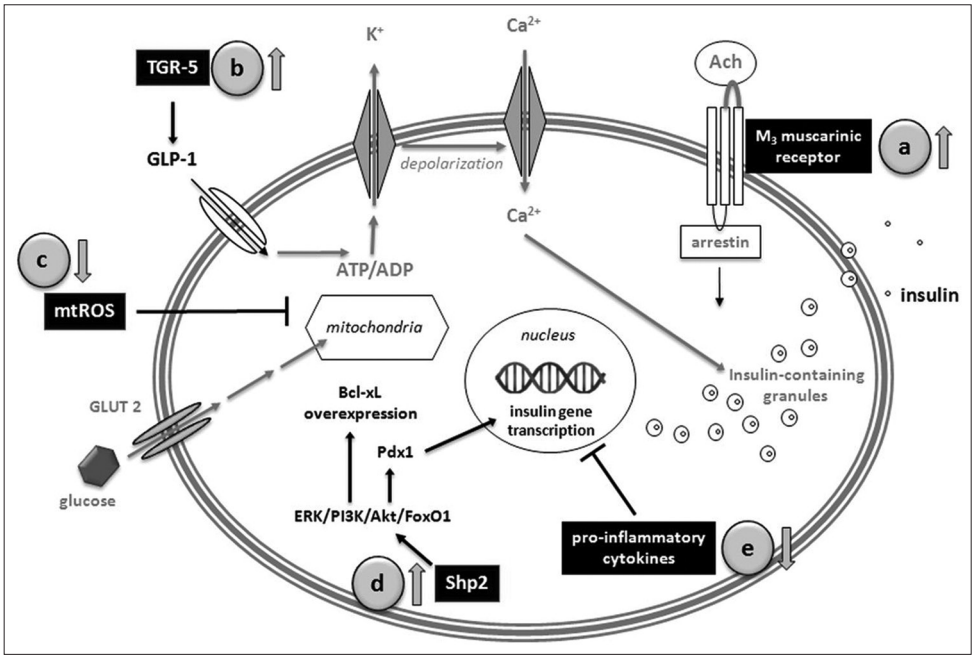

Figure 4: The role of oleic acid in insulin biosynthesis and secretion and improved glucose tolerance (taken from J. M. Castellano *et al.* Diabetes, vol. 62, no. 6, Jun. 2013)

of mastic gum [Table 4]. In diabetes patients there is myenteric inflammation with low grade inflammation in the duodenal mucosa that decreases permeability and hampers the micronutrient absorption from the small intestine.[35-37] Improvement in GI tract inflammation and gastroparesis symptoms such as vomiting, nausea and abdominal fullness leads to increased GI tolerance and micronutrients absorption. There was a significant reduction in Alkaline phosphatase (ALP) levels in Group A arm patient with no deterioration in liver functions and renal functions, which ensured probable renal and liver safety.

Conclusion

To our knowledge, this is the first study to compare the effect of levosulpiride (a pro-kinetic agent) with mastic gum in improving DG using a radionuclide gastric emptying scintigraphy scan. Mastic gum is found to have significant change in 4 h emptying % and $T^{½}$ time of GE and GCSI score with minimum or no side effects compared to levosulpiride. Mastic gum also helps in significantly lowering HbA1c levels, haemoglobin levels, LDL levels and total cholesterol levels, with no hepatotoxic and nephrotoxic actions. However, a large sample size is needed for further evaluation of better outcomes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Acknowledgement

The authors thank Department of CFM, AIIMS Rishikesh for advice on experimental design and statistical analysis

Authors contribution

Ajaypal Singh- Formulation of plan, Ravi Kant- concepts and guidance, Rohit Raina- manuscript prepration , Vandana Dhingra- literature search, Rajeev Nema- manuscript review, Mukesh Chand Bairwa- design and guidance, Varsha Kanwar- data analysis, Rifika- statistical analysis, Sukhes Mukherjee- clinical studies, Anissa Atif Mirza- manuscript editing, Mayank Agarwal- definition of intellectual content.

References

1. El Sayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, *et al.* Summary of revisions: Standards of care in diabetes-2023. Diabetes Care 2023;46(Suppl 1):S5-9.
2. Asha MZ, Khalil SFH. Pharmacological approaches to diabetic gastroparesis: A systematic review of randomised clinical trials. Sultan Qaboos Univ Med J 2019;19:e291-304.
3. Tack J, Janssen P. Gastroduodenal motility. Curr Opin Gastroenterol 2010;26:647–55.
4. Krishnasamy S, Abell TL. Diabetic gastroparesis: Principles and current trends in management. Diabetes Ther 2018;9(Suppl 1):1-42.
5. Abell TL, Bernstein RK, Cutts T, Farrugia G, Forster J, Hasler WL, *et al.* Treatment of gastroparesis: A multidisciplinary clinical review. Neurogastroenterol Motil 2006;18:263-83.
6. Li JL, Li M, Pang B, Zhou Q, Tian JX, Liu HX. Combination of symptoms, syndrome and disease: Treatment of refractory diabetic gastroparesis. World J Gastroenterol 2014;20:8674-80.
7. Bozorgi M, Memariani Z, Mobli M, Salehi Surmaghi MH, Shams-Ardekani MR, Rahimi R. Five Pistacia species (P. vera, P. atlantica, P. terebinthus, P. khinjuk, and P. lentiscus): A review of their traditional uses, phytochemistry, and pharmacology. Sci World J 2013;2013:219815.
8. Mahjoub F, Salari R, Yousefi M, Mohebbi M, Saki A, Rezayat KA. Effect of *Pistacia atlantica kurdica* gum on diabetic gastroparesis symptoms: A randomised, triple-blind placebo-controlled clinical trial. Electron Physician 2018;10:6997–7007.
9. Ben Ahmed Z, Yousfi M, Viaene J, Dejaegher B, Demeyer K, Heyden YV. Four Pistacia atlantica subspecies (atlantica, cabulica, kurdica and mutica): A review of their botany, ethnobotany, phytochemistry and pharmacology. J Ethnopharmacol 2021;265:113329.
10. Dabos KJ, Sfika E, Vlatta LJ, Frantzi D, Amygdalos GI. Is Chios mastic gum effective in the treatment of functional dyspepsia? A prospective randomised double-blind placebo controlled trial. J Ethnopharmacol 2010;127:205–9.
11. Mahjoub F, Akhavan Rezayat K, Yousefi M, Mohebbi M, Salari R. *Pistacia atlantica* Desf. A review of its traditional uses, phytochemicals and pharmacology. J Med Life 2018;11:180–6.
12. Kaliora AC. Chios mastic treatment of patients with active Crohn's disease. World J Gastroenterol 2007;13:748-53.
13. Giaginis C, Theocharis S. Current evidence on the anticancer potential of Chios mastic gum. Nutr Cancer 2011;63:1174-84.
14. Miyamoto T, Okimoto T, Kuwano M. Chemical composition of the essential oil of mastic gum and their antibacterial activity against drug-resistant Helicobacter pylori. Nat Prod Bioprospect 2014;4:227–31.
15. Assessment report on *Pistacia lentiscus* L., resina (mastic). Committee on Herbal Medicinal Products (HMPC 2 February 2016 EMA/HMPC/46756/2015). 2015. p. 1-14.
16. Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, *et al.* Gastroparesis cardinal symptom index (GCSI): Development and validation of a patient reported assessment of severity of gastroparesis symptoms. Qual Life Res 2004;13:833–44.
17. Almogbel RA, Alhussan FA, Alnasser SA, Algeffari MA. Prevalence and risk factors of gastroparesis-related symptoms among patients with type 2 diabetes. Int J Health Sci 2016;10:397–404.
18. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: A population-based survey of 15,000 adults. Arch Intern Med 2001;161:1989-96.
19. Jung HK, Choung RS, Locke GR 3rd, Schleck CD, Zinsmeister AR, Szarka LA, Mullan B, *et al.* The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, From 1996 to 2006. Gastroenterology 2009;136:1225–33.
20. Jones KL, Russo A, Stevens JE, Wishart JM, Berry MK, Horowitz M. Predictors of delayed gastric emptying in diabetes. Diabetes Care 2001;24:1264–9.
21. Boaz M, Kislov J, Dickman R, Wainstein J. Obesity and symptoms suggestive of gastroparesis in patients with type 2 diabetes and neuropathy. J Diabetes Complications 2011;25:325–8.
22. Sun J. D-Limonene: Safety and clinical applications. Altern Med Rev 2007;12:259–64.
23. Singh B, Sharma RA. Plant terpenes: Defence responses, phylogenetic analysis, regulation and clinical applications. 3 Biotech 2015;5:129–51.
24. Bharucha AE, Batey-Schaefer B, Cleary PA, Murray JA, Cowie C, Lorenzi G, *et al.* Delayed gastric emptying is associated with early and long-term hyperglycemia in type 1 diabetes mellitus. Gastroenterology 2015;149:330–9.
25. Groop LC, Luzi L, DeFronzo RA, Melander A. Hyperglycaemia and absorption of sulphonylurea drugs. Lancet 1989;334:129–30.
26. Melga P, Mansi C, Ciuchi E, Giusti R, Sciabà L, Prando R. Chronic administration of levosulpiride and glycemic control in IDDM patients with gastroparesis. Diabetes Care 1997;20:55–8.
27. Liu Z, Liu Z, Li Y, Guo J, Li J, Ren W, *et al.* Evaluation of gastric emptying by transabdominal ultrasound after oral administration of

semisolid cellulose-based gastric ultrasound contrast agents. Ultrasound Med Biol 2018;44:2183–8.
28. Castellano JM, Guinda A, Delgado T, Rada M, Cayuela JA. Biochemical basis of the antidiabetic activity of oleanolic acid and related pentacyclic triterpenes. Diabetes 2013;62:1791–9.
29. Kasabri V, Afifi FU, Hamdan I. *In vitro* and *in vivo* acute antihyperglycemic effects of five selected indigenous plants from Jordan used in traditional medicine. J Ethnopharmacol 2011;133:888–96.
30. Fukazawa T, Smyrnioudis I, Konishi M, Takahashi M, Kim HK, Nishimaki M, *et al.* Effects of Chios mastic gum and exercise on physical characteristics, blood lipid markers, insulin resistance, and hepatic function in healthy Japanese men. Food Sci Biotechnol 2018;27:773–80.
31. Kartalis A, Didagelos M, Georgiadis I, Benetos G, Smyrnioudis N, Marmaras H, *et al.* Effects of Chios mastic gum on cholesterol and glucose levels of healthy volunteers: A prospective, randomised, placebo-controlled, pilot study (chios-mastiha). Eur J Prev Cardiol 2016;23:722–9.
32. Berger J, Moller DE. The mechanisms of Action of PPARs. Annu Rev Med 2002;53:409–35.
33. Dedoussis GVZ, Kaliora AC, Psarras S, Chiou A, Mylona A, Papadopoulos NG, *et al.* Antiatherogenic effect of Pistacia lentiscus via GSH restoration and downregulation of CD36 mRNA expression. Atherosclerosis 2004;174:293–303.
34. Andrikopoulos NK, Kaliora AC, Assimopoulou AN, Papapeorgiou VP. Biological activity of some naturally occurring resins, gums and pigments against *in vitro* LDL oxidation. Phytother Res 2003;17:501–7.
35. Harberson J, Thomas RM, Harbison SP, Parkman HP. Gastric neuromuscular pathology in gastroparesis: Analysis of full thickness antral biopsies. Dig Dis Sci 2010;55:359–70.
36. Grover M, Farrugia G, Lurken MS, Bernard CE, Faussone-Pellegrini MS, Smyrk TC, *et al.* Cellular changes in diabetic and idiopathic gastroparesis. Gastroenterology 2011;140:1575-85.
37. Amerikanou C, Kanoni S, Kaliora AC, Barone A, Bjelan M, D'Auria G, *et al*. Effect of Mastiha supplementation on NAFLD: The MAST4HEALTH randomised, controlled trial. Mol Nutr Food Res 2021;65:e2001178.