IDDF2019-ABS-0231

EFFECTS OF A MIXTURE OF THE SEED OF SYZYGIUM JAMBOLANA, FRUITS OF MOMORDICA CHARANTIA AND LEAVES OF AZADIRACHTA INDICA PASTE ON LOPERAMIDE-INDUCED CONSTIPATION IN RATS

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10.1136/gutjnl-2019-IDDFabstracts.44

Background Constipation is one of the most common gastrointestinal complaints worldwide. Irritable bowel syndrome (IBS) is the most prevalent functional gastrointestinal disorders (FGIDs) that affects different aspects of life and patients experienced depression and anxiety more than others. The aim of this study is to evaluate the effects of a mixture of the seed of *Syzygium jambolana*, fruits of *Momordica charantia* and leaves of *Azadirachta indica* paste for the treatment of loperamide-induced constipation in a rat model.

Methods Animals were divided into one normal control group and three experimental groups (10, 20 and 30 g/kg). Loperamide (2 mg/kg, twice per day) was injected intraperitoneally to induce constipation in the three experimental groups. Each group of rats was given orally a dose of granules containing (10, 20 and 30 g/kg) concentrated ethanolic extract of a combined mixture paste from all three folk plants. Mixture paste was administered for 30 days to assess its anti-constipation effects.

Results Fecal pellet number, weight, and water content were increased in the plant mixture paste-treated groups as compared to the control group. Reductions in body weight and increased intestinal transit length were observed in the plant mixture paste-treated groups. Fecal pellet number was reduced in the distal colons of the plant mixture paste-treated rats. Exercise and ileum tension increased in the experimental groups as compared to the control group. According to histological analyses, the thickness of the distal colon and areas of crypt epithelial cells that produce mucin were increased in the treatment groups in a dose-dependent manner.

Conclusions Constipation was decreased when combined plant mixture paste was fed to rats. Specifically, fecal number, weight, and water content, as well as histological parameters such as thickness and mucin areas in the distal colon were improved. A mixture of *Syzygium jambolana*, *Momordica charantia* and *Azadirachta indica* is effective in eliminating IBS symptoms, and it is a related useful therapeutic and preventive strategy for chronic constipation.

IDDF2019-ABS-0235

METTL3 AS A POTENTIAL CANCER PROGNOSTIC MARKER PROMOTES THE PROLIFERATION AND METASTASIS OF GASTRIC CANCER CELLS

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10.1136/gutjnl-2019-IDDFabstracts.45

Background Gastric cancer serves as the fifth leading cause of malignancies, whose main cause of death is distant metastasis. Methyltransferase-like 3 (METTL3), a major component of N6-methyladenosine (m6A) methyltransferase complex, has been

suggested to function as an oncogene in several cancers. However, its clinical value and biological mechanism in gastric cancer remain unknown. Therefore, we attempted to investigate the expression profiles, prognostic value and possible downstream signal pathways of METTL3 in gastric cancer in this study.

Methods By analyzing data from the cancer genome atlas (TCGA), we depicted METTL3 expression profile and its possible downstream signal pathways in gastric cancer. Then, we further explored METTL3 expression and its prognostic values in 196 gastric cancers in our hospital. We established stable knock-down or overexpression of METTL3 gastric cancer SGC7901 cell lines to conduct *in vitro* and *in vivo* experiments.

Results METTL3 was significantly elevated in tumor tissues relative to normal gastric mucosa at both mRNA and protein levels. Moreover, the results from Kaplan-Meier survival curves analysis and multivariate Cox regression analysis demonstrated that METTL3 serves as an independent prognostic factor for gastric cancer patients. Furthermore, METTL3 can promote cell proliferation, colony formation, and cell migration and invasion. Additionally, the results of gene set enrichment analysis (GSEA) indicated that the potential downstream pathways of METTL3 were involved in cell cycle controlling. The top four pathways were as follows: the DNA repair pathway, the mitotic spindle pathway, the G2M checkpoint pathway and the E2F targets pathway.

Conclusions METTL3 was upregulated in gastric cancer and served as a promising prognostic biomarker for patients suffered this deadly disease. Moreover, METTL3 might play an oncogenic role in gastric cancer by the promotion of proliferation and invasion. The possible downstream pathways of METTL3 may be related to cell cycle controlling.

IDDF2019-ABS-0236

PATTERNS OF USAGE OF SUGAR-SWEETENED BEVERAGES (SSBs) AND THE ASSOCIATED BEHAVIORS WITH EXPENDITURE INCURRED AMONG PERSONS VISITING THE GENERAL OUTPATIENT DEPARTMENT OF A TERTIARY CARE HOSPITAL

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10.1136/gutjnl-2019-IDDFabstracts.46

Background The burden of non-communicable diseases in India has already reached epidemic proportions. Sugar-sweetened beverages (SSBs) are implicated in causing obesity, diabetes and cardiovascular diseases. There is a lack of data from India regarding how frequently and how much sugary drinks are consumed, in what forms, what are the associated behaviors and expenditures incurred due to consumption of SSBs.

To document the prevalence and patterns of usage of SSBs, associated behaviors and expenditure incurred among persons visiting the general outpatient department of a tertiary care hospital. **Methods** This was a cross-sectional study conducted in a public tertiary care hospital located in Bhopal in central India, between May and September 2018. Patients and accompanying persons attending the general out-patient department and who were ≥ 15 years of age were included. Patients who are severely ill were excluded. Convenience sampling was used to select participants. Exit interviews using a semi-structured interview schedule were conducted with subjects giving informed consent and after patients had completed the physician consultation.

Data were entered in Epi Info version 7.2 and analyzed using IBM SPSS version 22.

Results A total of 503 subjects were interviewed, out of which, 408 (81.1%) were males and 95 (18.9%) were females. Mean (SD) age of the subjects was 28.8 (10.7) years. Most subjects i.e. 387 (76.9%) resided in urban areas. Most were graduate or postgraduate i.e. 237 (47.1%), and almost half i.e. 50.1% were currently unemployed. Median (IQR) family income was Rs 30,000 (38,000).

Out of 503, 229 (45.5%) subjects had consumed SSBs in the last week, and another 135 (26.8%) had consumed it in the last month (but not within the last week). Median (IQR) consumption of SSBs in one year was 4800 (14600) ml. Almost half of them i.e. 250 (49.5%) had a preference for soft drinks, which was followed by 187 (37.2%), who preferred sweetened packaged fruit drinks. Only 64 (12.7%) checked for calorie content before consumption.

Conclusions Although most subjects had the knowledge that SSBs are harmful to health, the consumption and expenditures on SSBs were high.

IDDF2019-ABS-0245

SUPPRESSION OF FUMARATE HYDRATASE ACTIVITY INCREASES THE EFFICACY OF CISPLATIN-MEDIATED CHEMOTHERAPY IN GASTRIC CANCER

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10.1136/gutjnl-2019-IDDFabstracts.47

Background Gastric cancer (GC) is one of the most common malignancies worldwide. Due to the low rate of early detection, most GC patients were diagnosed at advanced stages and had a poor response to chemotherapy. Some studies found that Fumarate hydratase (FH) participated in the DNA damage response and its deficiency was associated with tumorigenesis in some cancers. In this study, we investigated the relationship between FH and cisplatin (CDDP) sensitivity in GC cell lines.

Methods We examined the role of FH for CDDP sensitivity in GC cells. Immunoblotting, qPCR, MTS were used to verify the relationship between FH expression and CDDP sensitivity. GC cells with FH knockdown were treated by CDDP and the apoptotic indexes were measured. Then we used FH inhibitor-Miconazole Nitrate (MN) to study the role of FH on GC cell death induced by CDDP. CDDP-induced apoptosis was quantified by immunoblotting and flow cytometric analysis. The role of FH on CDDP-induced DNA damage was evaluated using electrophoresis, comet assay and immunofluorescence. The synergistic effect of MN with CDDP on GC was measured on GC cells, cell line-derived xenografts, and patient-derived xenograft (PDX) model.

Results We found that FH was the most significant gene which induced by CDDP treatment and the suppression of FH could enhance the cytotoxicity of CDDP. MN could inhibit FH activity and enhance the effect of CDDP in vitro and in vivo. We also investigated the significance of expression of FH in GC tissues. The FH expression, which was higher in GC tissues than in noncancerous tissues, was negatively associated with the prognosis of patients.

Conclusions In summary, we demonstrated that FH is a reliable indicator for response to CDDP treatment in GC and the

inhibition of FH may be a potential strategy to improve the effects of CDDP-based chemotherapy.

IDDF2019-ABS-0246

LNCRNA XIST REGULATED CHEMOTHERAPEUTIC SENSITIVITY OF MIR-125B-2-3P BY TARGETING WEE1 IN COLORECTAL CANCER

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10.1136/gutjnl-2019-IDDFabstracts.48

Background Accumulating evidence has demonstrated that microRNAs regulate diverse tumorigenic processes, and play important roles in tumor metastasis and growth. Recently, miR-125b-2-3p was identified as a meaningful prognosis factor predicting the chemotherapeutic sensitivity in advanced colorectal cancer (CRC). However, the biological function and molecular mechanism of miR-125b-2-3p in chemotherapy of advanced CRC are urgent to explain.

Methods MiR-125b-2-3p expression was detected by real-time PCR (RT-PCR) in CRC tissues. The gain-of-function experiments were performed to assess the effect of miR-125b-2-3p on CRC growth, metastasis, invasion and drug sensitivity *in vitro* and *in vivo*. The prediction of the database has determined the competitive endogenous RNAs (ceRNAs) and target gene, which has confirmed by bioinformatic analysis, luciferase reporter assays, rescue experiments and western blot assays.

Results MiR-125b-2-3p expression was significantly downregulated in CRC tissues and cell lines. The high expression of miR-125b-2-3p was correlated with lower growth ability and metastasis. In addition, miR-125b-2-3p overexpression remarkably improves the chemotherapeutic sensitivity *in vitro* and *in vivo*. Mechanistically, miR-125b-2-3p was regulated by competitive endogenous RNAs, LncRNA-XIST, and influenced the expression of WEE1 G2 checkpoint kinase (WEE1). Upregulation of miR-125b-2-3p would reverse CRC growth and EMT process caused by LncRNA XIST by rescue analysis.

Conclusions Low expression of miR-125b-2-3p in CRC was linked to lower chemotherapeutic sensitivity and poor survival. LncRNA XIST would promote CRC invasion and migration by functioning as a ceRNA for miR-125b-2-3p to mediate WEE1 expression. Our finding suggested that miR-125b-2-3p may serve as a potential marker of chemotherapeutic sensitivity in CRC patients.

IDDF2019-ABS-0248

ASTRAGALUS POLYSACCHARIDE PROMOTES ADRIAMYCIN-INDUCED APOPTOSIS IN GASTRIC CANCER CELLS

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10.1136/gutjnl-2019-IDDFabstracts.49

Background As a polysaccharide, astragalus polysaccharide (APS) is extracted from the radix of astragalus membranaceus, a commonly applied herbal compound in traditional Chinese medicine. APS has been reported to increase tumor response, stabilize and reduce chemotherapy toxicity, and improve performance status.