SUPERIOR EFFICACY AND LONG-TERM TERMINALIA ARJUNA BARK EXTRACT was blocked by serum 4 weeks, TAB extract (300 mg/kg per day) continuously for rats. Arjuna bark (TAB) extract, composed mostly of ellagitannins induced liver injury. Arjunolic acid (AA) is an oleanane triterpenoid found mainly in the heartwood of Terminalia arjuna. Oxidants have been shown to be involved in the alcohol-induced liver injury. Combining the MHBs’ methylation scores as classifiers and applying RF method, we trained and cross-validated binary predictive models. Supervised analyses identified 65 MHBs as classifiers for HCC tissues and adjacent normal liver tissues. Both RF- and SVM-built models were highly accurate in classifying HCC and normal liver tissues with AUC no less than 0.98 (AUC: 98%, CI: 97.3%–98.8% for RF model; AUC: 99.9%, CI: 99.9% ~ 99.9% for SVM model). We applied the RF-trained classification model to differentiate HCC plasma DNA from those of healthy controls, with AUC of 96% (CI: 95.1% - 96.9%). We further identified 6 MHL-quantified MHBs and 5 UMHL-quantified MHBs as classifiers for MVI- and MVI+ samples. Combining the MHBs’ methylation scores as classifiers and applying RF method, we trained and cross-validated MVI- and MVI+ classification models. The result indicates that the TAB extracts exhibit antioxidant activity through correction of oxidative stress and validates the traditional use of Terminalia arjuna to prevents early alcohol-induced liver injury.

Background Terminalia arjuna, an indigenous plant used in ayurvedic medicine in India, primarily as a cardiotonic is also used in treating diabetes, anemia, tumors and hypertension. Oxidants have been shown to be involved in the alcohol-induced liver injury. Arjunicolic acid (AA) is an oleanane triterpenoid found mainly in the heartwood of Terminalia arjuna. This study was designed to determine whether Terminalia arjuna bark (TAB) extract, composed mostly of ellagitannins oligomers, protects against early alcohol-induced liver injury in rats.

Methods Total fifty-eight male Wistar rats were fed high-fat liquid diets with or without ethanol (10–14 g/kg per day) and TAB extract (300 mg/kg per day) continuously for 4 weeks using an enteral feeding protocol.

Results Mean body weight gains (approximately 4 g/day) were not significantly different between treatment groups. TAB extract did not affect average daily urine ethanol concentrations (approximately 200 mg/dL). After 4 weeks, serum alanine amino transferase levels of the ethanol group were increased nearly fourfold (110±16 IU/L) compared to control values (35±3 IU/L); this effect of ethanol was blocked by TAB extract (60±6 IU/L). Additionally, enteral ethanol caused severe fat accumulation, mild inflammation, and necrosis in the liver; TAB extract significantly blunted these changes. Increases in liver TNFalpha protein levels caused by ethanol were completely blocked by TAB extract. Further, ethanol significantly increased the accumulation of protein adducts of 4-hydroxyynonenal, a product of lipid peroxidation serving as an index of oxidative stress; again this was counteracted by the addition of TAB extract.

Conclusions The result indicates that the TAB extracts exhibit the antioxidant activity through correction of oxidative stress and validates the traditional use of Terminalia arjuna to prevents early alcohol-induced liver injury.

Background The heterogeneous responses to immune-checkpoint blockade (ICB) therapy e.g. anti-programmed death-ligand 1 (PD-L1) antibody are attributable to the complex interplay between a range of cancer-cell-autonomous cues and immunosuppressive tumor microenvironment. Two recent phase I/II trials of PD-1 checkpoint inhibitors in patients with advanced hepatocellular carcinoma (HCC) have produced promising results, yet the objective response rates were relatively low (<20%). Accumulating evidence underscores the fundamental importance of epigenetic regulation in tumor immune evasion. We have previously elucidated a critical role of histone deacetylase 8 (HDAC8) in hepatic carcinogenesis (Cancer Research 2015;75:4803–16). Here, we aim to investigate the therapeutic potential of a HDAC8-specific inhibitor PCI-34051 in preclinical HCC models.

Methods The effect of PCI-34051 on tumorigenicity was investigated in orthotopic HCC mouse models. Immune profiling in tumor microenvironment was determined by multi-color flow cytometry. The underlying mechanism was investigated by integrative epigenomics analysis. The anti-tumor efficacy of combined therapy with PCI-34051 and anti-PD-L1 antibody was further determined.

Results PCI-34051 significantly suppressed tumorigenicity in immunocompetent but not immunodeficient mice, which was accompanied by increased effector T cell tumor infiltration. Mechanistically, tumor-intrinsic HDAC8 epigenetically silenced chemokine CCL4 expression via H3K27 deacetylation at the enhancer to inhibit T cell infiltration to tumor. Furthermore, PCI-34051 dramatically improved the therapeutic efficacy of