division activation. PFD increases apoptotic markers expression (Cas-3), tumor suppressors (p53) and re-establishes proteins in cellular metabolism regulation (PPARalpha/PPARgamma).

Conclusions: PFD administration prevents chemical-induced carcinogenic damage in MMRH. PFD decreases fibrotic and proinflammatory markers; likewise, PFD regulates tumor suppressor and mitogenic markers.

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Analysis of the molecular interaction of pirfenidone with PPAR-gamma and effects on the beta-catenine pathway in HEPG2 line

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Background and aim: PPARgamma is a nuclear receptor that regulates genes involved in energy metabolism. It consists of a transactivation domain at the N-terminus, two zinc fingers required for DNA binding, and a ligand-binding domain at the C-terminus that facilitates RXR-alpha binding and activation. The interaction of PPARgamma/beta-catenin has recently been established in type 2 diabetes and the development of colon cancer. On the other hand, Pirfenidone (PFD) has shown antifibrotic, anti-inflammatory, and antioxidant effects in various models of liver damage. The objective of our work was to demonstrate by *in silico* analysis that PFD is a ligand/agonist of PPARgamma and subsequently analyze the activity of beta-Catenin in the HepG2 hepatocarcinoma cell line.

Material and methods: Molecular interaction analysis was performed using the SwissDock platform, the images were made with the 3D UCSF CHIMERA processor. For in vitro analysis, the HepG2 cell line was used. The cells were treated with 500 μM PFD, the non-selective agonist (GW7647; 100 nM) and the selective antagonist (GW9662; 100 nM) of PPARgamma for 24 hrs. Immunofluorescence and Western-Blot of PPAR gamma and beta-Catenin were performed. The experiments were carried out in triplicate, GraphPadPrism 7 was used to prepare the graphs and statistical analysis.

Results: *In silico* analysis shows that Pirfenidone binds to the Serine342 residue of PPARgamma, the same site that Rosiglitazone binds to. Immunofluorescence shows increased PPARgamma placement and lower beta-Catenin in the nucleus for cells treated with PFD and GW7647. The opposite is observed in control and GW9662-treated cells. There is a differential expression of PPARgamma and beta-Catenin in cells treated with PFD and GW7647.

Conclusions: PFD is a ligand /agonist of PPARgamma because it binds to the Serine342 residue, just as Rosiglitazone does (a pharmacological agonist used in the treatment of type 2 diabetes mellitus). Additionally, treatment with PFD in HepG2 cells decreases the translocation of beta-Catenin to the nucleus, which could contribute to slow the progression of HCC.

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Prolonged-release pirfenidone prevents myocardial fibrosis in a mouse nonalcoholic steatohepatitis model

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Background and aim: Obesity is associated with insulin resistance, nonalcoholic steatohepatitis (NASH) and myocardial fibrosis. Peroxisome proliferator-activated receptors (PPARs) regulate carbohydrate and lipid metabolism; improving insulin sensitivity, triglyceride levels, inflammation and oxidative stress. Pirfenidone has anti-inflammatory, antioxidant and antifibrotic effects. Aim, we investigated the molecular effects of prolonged-release pirfenidone (PR-PFD) in ventricular tissue of male C57BL/6J mice with NASH.

Material and methods: All experiments were performed in compliance with the guidelines of the bioterium-CUCS Research Committee at the University of Guadalajara and National Institutes of Health (NIH). Five-week-old mice were fed with normal diet (ND, 18% kcal from fat, $n = 5$) and high-fat/high-carbohydrate (HFHC, 60% kcal from fat, plus 42 g/L: 55% fructose y 45% sucrose in water, $n = 10$) diet for 16 weeks of feeding. At 8 week, five mice with HFHC diet were administered PR-PFD (350 mg/kg/day). We assessed insulin resistance, oil red o, hematoxylin-eosin, Masson's trichrome and picrosirius staining, western blot, immunohistochemistry, RT-qPCR and data by SPSS.

Results: Mice showed NASH with insulin resistance, myocardial steatosis and fibrosis, which were prevented by PR-PFD. Ventricular tissue of HFHC mice showed increased TNF-α, Nrf2, Desmin, Tgfβ1, Timp1, Collagen-I, Collagen-III, mRNA levels, including NF-kB, Nrf2, α-SMA, Troponin-I, Acox1, Cpt1A and Lxrα protein levels compared to the ND ventricular tissues ($P \leq 0.05$). PR-PFD treatment decreased these genes overexpressed by HFHC diet ($P \leq 0.05$). PR-PFD overexpressed the Pgc1a mRNA levels and Pparα, Pparγ, Acox1 and Cpt1A protein levels ($P \leq 0.05$).

Conclusions: PR-PFD prevents the cardiac steatosis and fibrosis by sobreexpressing Pparα, Pparγ, Acox1 y Cpt1A proteins. PR-PFD is a promising drug for the treatment of cardiac fibrosis induced by NASH.

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