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A Multi Gene Targeting Approach to Treating Liver Diseases with Metadichol®

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Received date: December 27, 2018; Accepted date: January 07, 2019; Published date: January 14, 2019

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Abstract

Liver diseases are becoming a major health concern. In the developing countries it is due to microbial infection. In the rest of the developed world it is due to alcohol abuse. Chronic liver disease and cirrhosis are a significant health concern in western countries. It is the fifth most common cause of death, after heart disease, cancer, stroke, and chest disease. The liver is capable of regeneration, but it can be overwhelmed leading to liver diseases like cirrhosis and hepatocellular cancer (HCC).

Vitamin D levels are low in most patients with liver diseases, and this suggests possible therapeutic benefits with use of vitamin D or its analogues. Vitamin D, through the vitamin D nuclear receptor (VDR) plays a crucial role in mineral ion homeostasis. The liver has a central role in vitamin D synthesis and there is a need for an agent that will not lead to hypercalcemia. Metadichol, a nano emulsion of long-chain alcohols derived from food, is an inverse agonist of Vitamin D can fill this void.

In Diabetic rat studies, it inhibits TNF alpha, ICAM1 (intracellular adhesion molecule), CCL2 (chemokine C-C motif) also referred to as monocyte chemoattractant protein 1 (MCP1). All these cytokines, chemokines are known to have important role in liver diseases. We show that Metadichol indeed does work in liver disease patients by normalizing essential liver enzymes ALT, AST and ALP, and GGT. This approach is an example where Metadichol targets multiple genes and *via* multiple pathways to bring about homeostasis of the liver and is a useful, safe, non-toxic product in treating liver diseases and alleviating a global threat.

Keywords: Liver; Cirrhosis; Hepatocellular cancer; Hepatic failure; NAFLD; NASH; TNF; CCL2; MCP1; PAI1; ICAM1; Inverse agonist; VDR; Gilbert syndrome

Abbreviations: NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Nonalcoholic Steatohepatitis; TNF: Tumor Necrosis Factor; CCL2: Chemokine Ligand 2; MCP1: Monocyte Chemoattractant Protein 1; PAI1: Plasminogen Activation Inhibitor; ICAM1: Intercellular Adhesion Molecule 1; VDR: Vitamin-D Nuclear Receptor; ALD: Alcoholic liver Disease.

Introduction

Liver diseases are a worldwide problem. The number of drugs for treating liver diseases is small in number. There is a need for a safe and therapeutic treatment with new molecular entities [1,2,3].

The liver helps purify the blood. It produces albumin as well as the proteins that cause blood clotting. The liver stores sugar fats and vitamins until they are needed elsewhere in the body and also manufactures fat, cholesterol, and protein bilirubin. An inflamed liver does not perform these functions well, which brings about many of the symptom and problems associated with any hepatitis.

Liver diseases

NAFLD (Non-alcoholic fatty liver disease is a condition when there is an excess of fat in the liver of people who do not consume alcohol [4]. The standard form of NAFLD is a benign condition called fatty

liver when fat accumulates in the liver cells. NAFLD leads to hepatic steatosis NAFL (Nonalcoholic fatty liver disease), and affects about 20% of patients and also is present in type 2 diabetes patients.

NASH [5] is a condition where the liver sustains substantial damage, and the liver cells are gradually replaced by scar tissue impairing liver function. Some patients who develop cirrhosis may eventually require a liver transplant to remove the damaged liver.

Hepatitis A B and C are viruses [6] that can impair liver function. The diseases caused by them are similar and lead (7) to liver inflammation that can be severe or even life-threatening. There are effective vaccines for hepatitis A and B but not for type C. Liver failure and hepatocellular carcinoma (HCC) are caused by alcohol abuse and obesity the leading causes of chronic liver diseases especially in the developed world.

In advanced liver diseases, Perez et al. [7] showed that liver cirrhosis is caused by HBV/HCV infection. Prevention of liver cirrhosis and HBV/HCV infection is necessary as HCC can result. The solution is to avoid alcohol, and drugs but treating the underlying causes i.e. alcoholism and HBV/HCC related infections.

HCC [8] is a serious problem because no treatment is available. The underlying causes for development of HCC are type 2 diabetes, alcoholism and chronic HBV/HCV infections that can lead to liver cirrhosis.

Nuclear receptors, cytokines, chemokines and liver diseases

Nuclear receptors (NRs) express genes that are involved in clearing toxic biliary constituents that are the hall mark of cholestasis [9]. Activation of NRs like VDR and FXR modulates many biological processes like inflammation and carcinogenesis. Break down of NR signaling leads to cholestasis disorders. NRs activation has the potential to modulate processes in cholestatic liver diseases [10]. Drugs used today exert their beneficial effects in cholestasis via NR activation for e.g. FXR activation (obeticholic acid) [11].

VDR activation in liver cells leads to anti-inflammatory and anti-fibrotic effects [12]. Targeting of VDR leads to improved bone density. Cholestasis leads to low vitamin D levels in Osteoporosis. 1, 25-Vit D3 actions on VDR results in reduced fibrosis in rat [13] and also lowered levels of pro-inflammatory cytokines in mice studies [14]. Vitamin D supplementation can help patients with liver diseases.

TNF α

Cirrhosis is considered an advanced stage of liver fibrosis. It causes over 1 million deaths per year, being the 14th leading cause of death worldwide [15]. Liver fibrosis leads to accumulation of collagen, elastin, and fibronectin, a consequence of hepatocyte death because of liver inflammation [16]. Serum levels of TNF- α is directly related to the severity of hepatic dysfunction in liver Cirrhosis [17]. TNF α enhances HSC (Hepatic stellate cells) survival leading to enhanced liver fibrosis. TNF alpha inhibitors in the market today have serious side effects [18,19]. Clinical trials using anti-TNF α antibody have failed in alcoholic hepatitis [20]. Therefore, targeting of specific TNF α signaling pathways could be considered as a new therapeutic approach for the liver fibrosis.

ICAM1

Intercellular adhesion molecule 1 (ICAM-1) belongs to immunoglobulin supergene family that promotes intercellular adhesion. Present on the cell surface glycoprotein it is an important early marker of response to inflammatory mediators and immune activation [21,22].

Capra et al. [23] showed that patients with chronic HCV-related hepatitis have higher levels of sICAM-1 than do control subjects. The increase in sICAM-1 level is a result of HCV activity, which damages both hepatocytes and sinusoidal vessels [24] and, in particular, endothelial cells. Inflammation and cytolysis lead to an up regulation in the expression of tissue ICAM-1, which is mediated by proinflammatory cytokines [25,26].

In knockout mice ICAM-1 and infiltrating leukocytes play essential roles in early alcohol-induced liver injury [27]. They suggest that it is most likely caused by free radicals from NADPH oxidase in the Kupffer cell increasing NF- κ B activation, that induces ICAM-1 expression via mechanisms involving TNF- α .

Chen et al. [27] showed that ICAM-1 is a critical biomarker associated with development of future HCC incidence in chronic liver disease in patients with various chronic liver diseases that were free of HCC at baseline. Their findings held across diverse etiologies of liver disease and in patients with and without cirrhosis, were independent of established clinical risk factors.

CCL2

CCL2 (also called as MCP1) is a chemokine involved in immunoregulatory and inflammatory processes in the development of several acute and chronic liver diseases, inflammation and regulation of immune response. Chemokines have been shown to regulate diverse conditions such as cardiovascular diseases and cancer [28]. Expression of CCL2 results in the infiltration of monocytes that predominately express the receptor CCR2.

In liver diseases CCL2 and CCR2 levels are high and results in increased inflammation, fibrosis, and steatosis [29]. Continuing inflammation leads to chronic liver diseases, like hepatitis C and non-alcoholic steatohepatitis. CCL2 has a role in alcohol-related damage, because its liver and plasma levels were associated with disease severity and with inflammation, including neutrophil infiltration, but not with steatosis, in patients with the alcoholic liver disease. [30,31]. Plasma levels and hepatic expression of CCL2 have been shown to be increased in ALD (alcoholic liver disease) patients. CCL2 over-expression is associated with parameters of disease severity in all liver diseases. Activation of pro-inflammatory pathways induced by alcohol was controlled in CCL2-deficient mice. Besides genes of fatty acid metabolism were induced in livers of alcohol-fed CCL2-KO mice, [32,33,34].

PAI1

PAI-1 (also known as SERPINE1) is the primary inhibitor of plasminogen activators playing a significant role in fibrinolysis [35]. PAI-1 has a major role in mediating fibrosis during cholestasis. Hyperfibrinolysis and hypo-fibrinolysis are the result of elevated PAI-1 levels and also the development of alcoholic liver disease (ALD). This results in inflammation, and necrosis (steatohepatitis), and ultimately leads to fibrosis and cirrhosis. Inhibition of PAI-1 could mitigate alcohol-induced liver damage fibrosis and cirrhosis. It has been shown that hepatic fibrosis is eliminated in mice that are deficient in PAI-1 [36].

No therapy is available to treat ALD. Treatment goal is on reducing effects of disease and or transplantation of livers of individuals with terminal cirrhosis. Hepatic steatosis can be blocked by inhibiting PAI-1 activation [37]. PAI-1 level is an indication of the disease severity [38].

Initially Hepatic changes caused by alcohol lead to steatosis. That initiation, then leads to ALD [39]. For example, in fatty livers the degree of fatty infiltration correlates with severity of ALD, fibrosis and cirrhosis [40,41]. Steatosis is caused by alcohol metabolism [42] that induces (TNF- α production which up regulates PAI-1 expression) [43].

Gilbert syndrome a liver disorder that results when the body cannot process bilirubin a waste product of red cells [44] caused by structural liver damage. This results in elevated levels of bilirubin caused by a lack of liver enzymes needed for elimination of bilirubin [45,46,47].

Individuals may only exhibit mild yellowing of the skin and whites of the eyes (jaundice). Gilbert syndrome is seen more often in males than females. The disorder affects approximately 6-7% of individuals in the general population. Gilbert syndrome affects individuals of all races. Similar to Gilbert's syndrome are Crigler-Najjar, Rotor syndrome and Dubin-Johnson syndrome. All these are disorders are due to high levels of bilirubin in the blood [48].

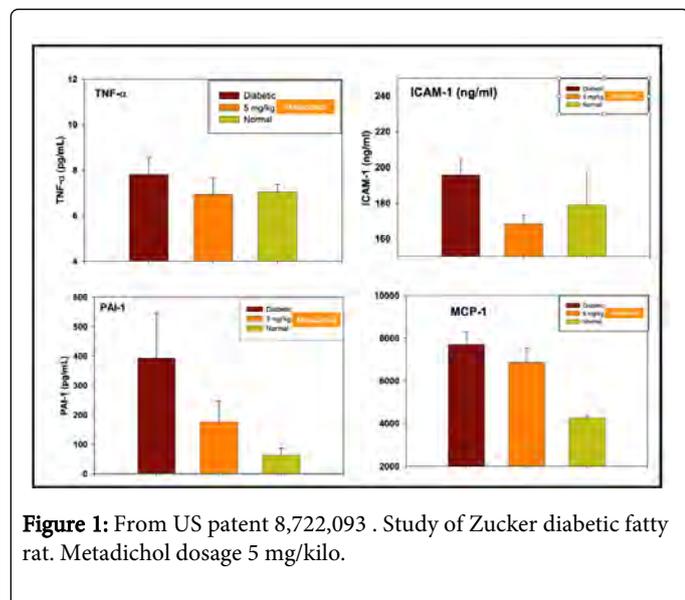
Levels of liver enzymes serum aminotransferases alanine and aspartate aminotransferases (ALT and AST), alkaline phosphatase

(ALP) and gamma-glutamyltransferase (GGT) [49,50,51] is what are used to detect liver diseases and their severity. A high level of serum ALT, AST is directly related to damaged liver tissues. In Alcoholic liver disease the AST:ALT ratios are used in determining presence of damaged liver diseases [52].

Alkaline phosphatase levels has a serum range of 20 to 140 U/L. The ALP test is used in identifying conditions such as hepatitis, cirrhosis, inflammation of the gallbladder blockage of bile ducts (from a gallstone, inflammation, or cancer). The enzyme alkaline phosphatase is a vital serum analyte, and its elevation in serum is seen in bone, liver and other diseases [53] ALP levels lead to bile ducts obstruction. Elevated ALP levels could indicate hyperparathyroidism, vitamin D deficiency, or damaged liver cells [54]. Levels are elevated in people with untreated Celiac disease [55]. Over expression of ALP is seen in cancer patients [55,56], tumorigenesis [57,58] and also in breast cancer patients [59-62]. The number of drugs for treating useful liver drugs is small that there is a void that needs to be filled for safe and efficient therapeutic agents [63]. Compounds and or extracts from plants have been used in targeting liver diseases liver but have not been well studied and there is a need for additional research to justify their use in as it relates so safety and efficacy. Steroids have been used but have failed to show any significant results [64].

IFN- α treatment in viral hepatitis is the standard of care today [65]. It has a drawback as serious side effects such as depression and also nephrotic syndrome, retinal ischemia and decreased visual acuity have been reported. No FDA-approved drug treatment exists for the nonalcoholic fatty liver disease.

Metadichol® is a nano emulsion of long chain alcohols derived from food-based sources. It is safer than salt and sugar and has no known reported side effects. We have shown that it is a TNF α , ICAM1, CCL2 (also known as MCP1) and PAI1 (Serpine1) inhibitor (Figure 1).



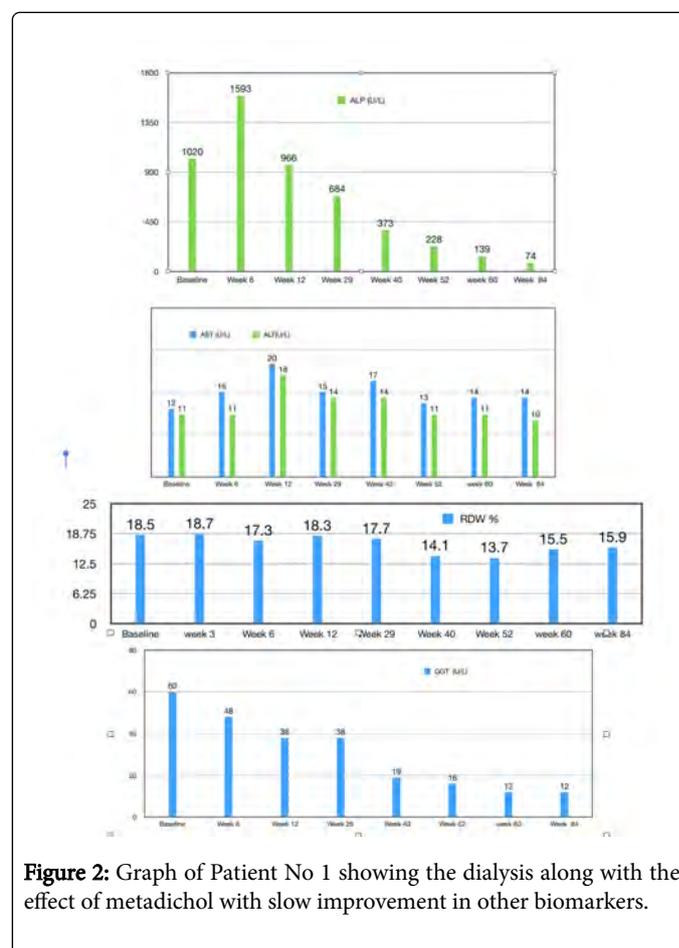
We have shown that it binds to Vitamin D receptor as an inverse agonist [66]. Given the importance of these cytokines/chemokines described above in liver diseases, we present case studies to confirm its effects on liver diseases.

Case Studies

Patient No. 1

A 29-year-old female on kidney dialysis for last 9 years after first child birth. Not on any liver medication, very high Alkaline Phosphatase levels and elevated GGT levels. Treated with Metadichol @ 5 mg daily.

Twice a day, her ALP levels increased in the first weeks before a steady decrease began over the next few weeks. There were also other improvements in her biomarkers RDW (Red Cell Distribution Width) which we have documented in other kidney patients [67]. Patient is still on dialysis as she awaits a donor and showing slow but steady improvement in other biomarkers (Figure 2).



Patient No 2

A 25-year-old Male diagnosed with Autoimmune Hepatitis and possibly primary sclerosing cholangitis (PSC) since the age of 15 with elevated ALP, AST and ALT levels (Figure 3). Suffered from GI and food allergies and repeated colon infections. He Tried various treatments with drugs like prednisone and Imuran and Remicade all were of no use. Having tried and failed with known therapies the patient started on Metadichol orally @ 5 mg twice a day. Patient was on no other treatment, during this 12 week treatment. The patient reports improved energy levels, and for the first time in 10 years, his

AST and ALT returned to normal. He underwent a liver transplant soon after and is now normal.

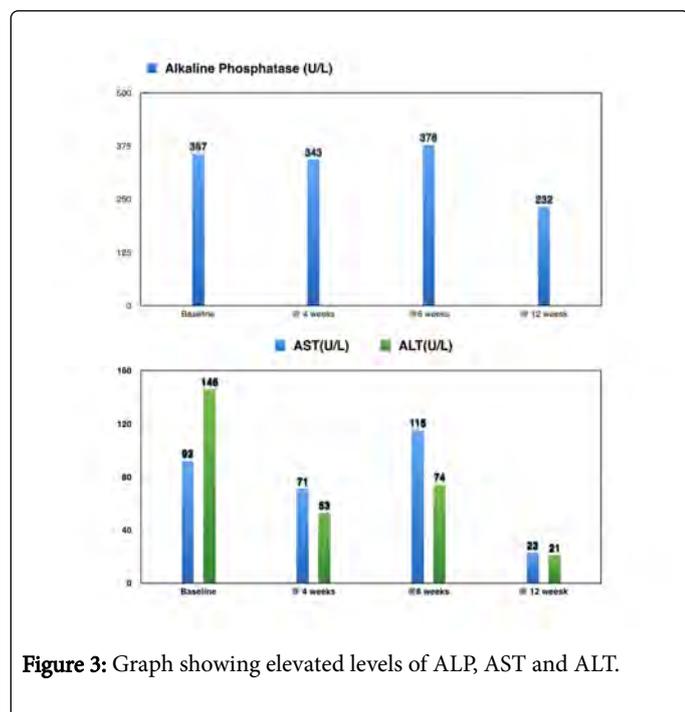


Figure 3: Graph showing elevated levels of ALP, AST and ALT.

Patient No 3

A 47-year-old female diabetic for 6 years mildly elevated liver enzymes. Metadichol treatment 5 mg twice a day. The liver biomarkers returned to normal (Figure 4).

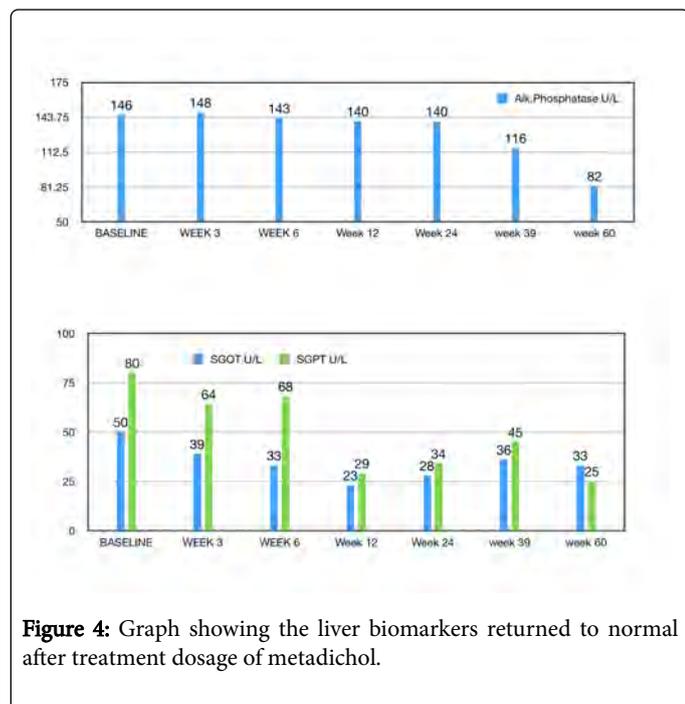


Figure 4: Graph showing the liver biomarkers returned to normal after treatment dosage of metadichol.

Patient No 4

A 35-year-old female, elevated levels of bilirubin, diagnosed as Gilbert's syndrome. Metadichol @ 5 mg twice a day. Her levels returned to normal in 24 weeks (Figure 5).

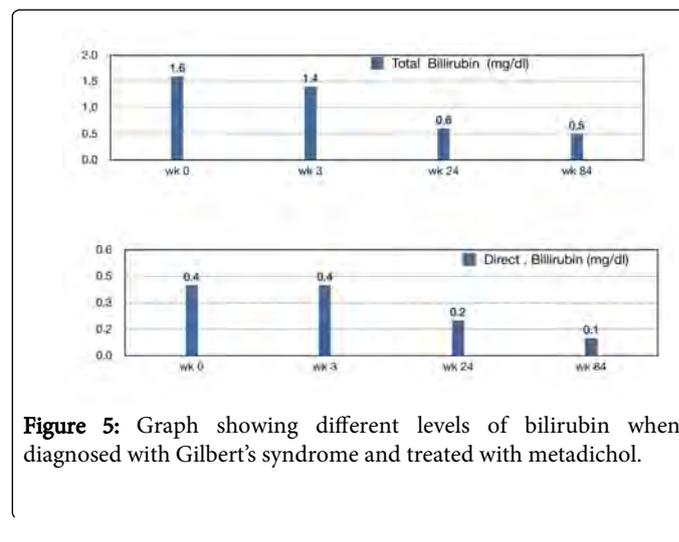


Figure 5: Graph showing different levels of bilirubin when diagnosed with Gilbert's syndrome and treated with metadichol.

Discussion and Conclusion:

The application of Metadichol in all the cases presented led to rapid normalization of the liver biomarkers suggests that it could be modulating diseases through multiple pathways, binding to VDR and activating innate immunity pathways and Inhibiting TNF alpha, ICAM1, and CCL2. Most of the known therapies for today target one gene and there is a need for a comprehensive targeting of clusters of genes to target liver and other diseases via multiple disease pathways multiple genes as shown in Figure 6.

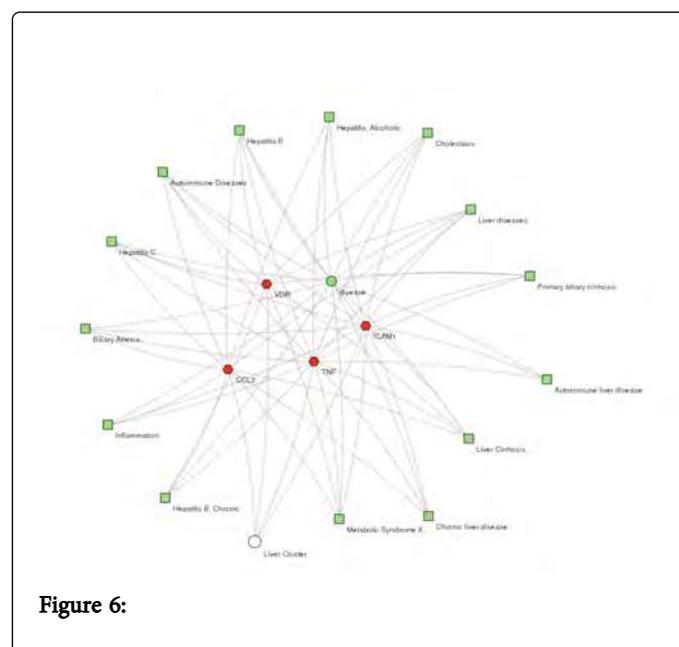


Figure 6:

Metadichol binding to VDR and inhibition of TNF, ICAM1 and CCL2 can be analyzed using a software program like ToppCluster [68,69] shows how these clusters of genes target many liver-related

diseases. Using Pathway Commons program [70] has one can further extend this approach by looking at the known experimentally curated interactions of TNF, ICAM1, and CCL2 shown in Figure 7. We see that IFNG (interferon gamma) is regulated by TNF, ICAM1, and CCL2. IFNG plays an important role in in lammation and autoimmune disease [71]. Increased levels of IFN- γ are directly related to liver disease severity [72] and were associated with the progression of liver disease [73]. T-helper cell (Th17) cells a subset of T cells are critical to in lammation [74]. VDR leads to a TH2 response, and Metadichol is a inverse agonist of ROR gamma thus blocking the Th17 pathway [74]. since CCL2, TNF and ICAM 1 are all inhibited and thus IFN gamma the whole process is driven towards a VDR driven Th2 pathway [75].

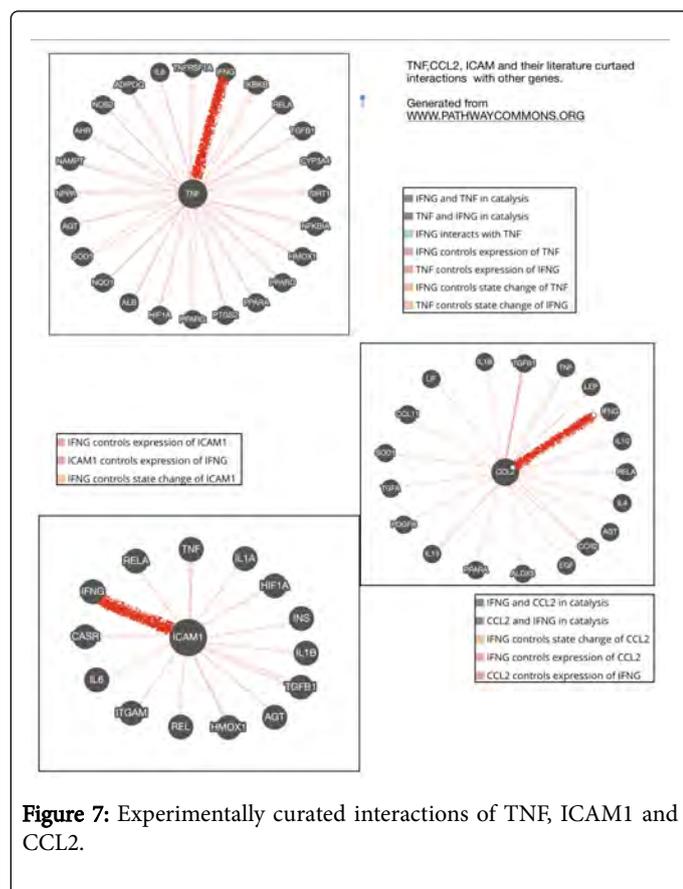


Figure 7: Experimentally curated interactions of TNF, ICAM1 and CCL2.

Diseases are connected through closely related gene networks, and this is an approach that can be exploited to modulate multiple targets to enhance therapeutic effect as ligands today are focused on a single target and limited by their efficacy. Metadichol is a safe therapeutic that target multiple genes, pathways and multiple diseases that confirms the relevance of network-based approach of poly-pharmacology [76] and this has been demonstrated by our studies on other diseases [77-91].

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