In the past few years, the incidence rate of hepatocellular carcinoma (HCC) has increased in the developing countries. Despite advances in imaging studies, surgical techniques and local, surveillance and detection are suboptimal for HCC and it remains as a very lethal cancer causing more than 745,000 deaths per year. Therefore there need a focusing point on the natural herbal products as anti cancer agent based on their therapeutic strategies. Citrus fruits have been widely recognized for their medicinal applications such as anti-inflammatory, anticarcinogenic, antiviral, antioxidant, antithrombogenic and antiatherogenic effects among others. The peel of citrus fruits has been used in traditional Asian medicine for centuries and it is a rich source of flavonoids and almost the sole source of polymethoxyflavones. The present study had been undertaken with the Citrus fruit name, *Citrus platymamma* hort. ex Tanaka, Korean name Byungkyool. Human hepatocellular carcinoma Hep3B cells were treated with 100 µg/ml of *Citrus Platymamma* extract. After 24 hour incubation, cells were harvested. The extracted proteins were assayed and resolved by 2DE using pH 3-10 IPG strips loaded with 200 µg of total protein. The significant differences in protein expression between control and citrus extract treated cells were analyzed by two-dimensional gel scanning and image analysis using Progenesis Samespots software (≥2 fold was considered significant). Based on the earlier achieved result on growth inhibition of Hep3B cells treated with citrus extract 100 µg/ml, the proteomics studies were performed. We had found a total of 7 statistically significant differentially expressed protein spots (≥2-fold and p<0.05). Out of these, 6 differentially expressed protein spots were chosen for further MALDI–TOF/MS analysis for protein identification. Based on the differentially expressed protein identification by MALDI-TOF/MS analysis using the MASCOT search engine and the SwissProt database would suggest the role of protein to signal pathways mechanism in Hep3B cells. These finding would suggest that the *Citrus platymamma* extract plays a therapeutic role in hepatocellular carcinoma.