Advanced Research in Gastroenterology & Hepatology
ISSN: 2472-6400

Juniper Publishers
key to the Researchers

Review Article
Volume 15 Issue 2 - June 2020
DOI: 10.19080/ARGH.2020.15.555907

Adv Res Gastroentero Hepatol


# Flavones as Potential Adjuvants for Therapeutic Treatments of Hepatocellular Carcinoma

**Raymond P Wu***

*Keck School of Medicine of University of Southern California, USA*

**Submission:** May 19, 2020; **Published:** June 01, 2020

***Corresponding author:** Keck School of Medicine of University of Southern California, 1333 San Pablo Street, Los Angeles, CA 90089, USA

**Abstract**

Hepatocellular carcinoma (HCC) is one of the most feared complications of liver disease due to its high mortality rate combined with lack of effective treatments, which at present are predominantly ablative and surgical. Current molecularly-targeted therapeutic treatments of HCC target common survival pathways of cancer cells and regenerating hepatocytes. Therefore, the combination treatment designed to eliminate drug-resistant tumor cells may be additionally toxic to hepatocytes. Since hepatocyte death promotes HCC, hepatotoxicity presents a challenge for successful HCC treatments. On the other hand, although cancer cell death reduces HCC burden, hepatocyte death exacerbates HCC development. Therefore, balancing hepatocyte death and cancer cell death is a key aim for successful HCC treatments. Consequently, small molecules enhancing cancer cell death without killing hepatocytes are potentially useful adjuvants of anti-HCC treatments. Flavones, plant-derived natural products, are potent adjuvants due to their cancer selective property. This commentary will discuss current challenges of HCC treatments and the potential use of flavones as adjuvants of HCC treatments.

**Keywords:** Hepatocellular carcinoma; Flavone; Cancer selectivity; Hepatocyte death; Baicalein

**Abbreviations:** HCC: Hepatocellular Carcinoma; mTORC: Mammalian Target of Rapamycin Complex; EpCAM: Epithelial Cellular Adhesion Molecule; CD: Cluster-of-Differentiation; TICs: Tumor-Initiating Cells; DEN: Diethylnitrosamine; TSC: Tuberous Sclerosis; MDR: Multidrug Resistant; PBMC: Peripheral Blood Mononuclear Cells; CLL: Chronic Lymphocytic Leukemia; ARE: Antioxidant Response Element

## Introduction

Cancer is the second leading cause of death among all diseases [1]. Although the cancer death rate is decreasing in the recent decade, the total number of cancer deaths is increasing, probably due to the expanding cohort of older individuals. In the past two decades, the death rate for numerous cancers has declined while the five-year survival rates of many cancer patients have improved substantially [1,2]. Although the number of people with liver cancer ranks twelfth among cancer patients worldwide, the death rate attributed to liver cancer ranks second among all cancers worldwide due to the lack of effective and safe treatments of liver cancer. Furthermore, liver cancer remains the second lowest cancer in terms of 5-year survival rate. These results highlight the observation that progress in the treatment of liver cancer has lagged behind that of other cancers. Its incidence has been increasing in recent years and is predicted to rise as people living with chronic liver diseases continue to age [3]. Other than tumor resection and orthotopic liver transplantation, there is currently no effective treatment. Even after receiving tumor resection and transplantation, tumor recurrence is inevitable.

Current efforts are focused on finding drug combinations that increase the chances of eliminating cancer recurrence. Yet, the major challenge of combination therapy in liver cancer is the additional toxicity caused by combination of drugs with different mechanisms. Hepatocellular carcinoma (HCC) contributes to 85-90% of all liver cancers. In experimental animal models, it is established that HCC cells are derived from chronically damaged hepatocytes [4,5]. Massive hepatocyte death promotes compensatory proliferation in the liver as well as inflammation. The activation of hepatocyte regeneration to replace hepatocytes may induce DNA damage and further predispose the chronically-injured liver to HCC due to DNA damage caused by replication stress [6]. Therefore, cytotoxic therapies that non-selectively kill cancer cells and hepatocytes may enhance liver injury, complicating successful therapeutic treatment. This conundrum is the principal reason why it is extremely hard to treat HCC with combination therapy. Therefore, treatments that induce additive or synergistic anti-oncogenic properties without causing additional toxicity would be desirable for HCC.

This commentary will argue for a new strategy to use molecules derived from nature, more specifically flavones, as complementary medicine to current anticancer drugs to prevent HCC recurrence. Flavones are present in fruits and plants commonly consumed

by humans in addition to serving as components of several traditional herbal medicines. These compounds have moderate anticancer activities, though insufficient for use as single agents. The primary advantage of flavones is that they are relatively non-toxic to normal cells. They accumulate in the liver and even protect the liver from damaging chemicals. Therefore, the combinatorial activity of flavones and anticancer agents to treat liver cancer holds promise.

## Tumor Recurrence in HCC

The most effective method to remove the tumor burden in liver cancer is tumor resection or liver transplantation. In HCC patients who have undergone liver transplantation, the risk of recurrence is inevitable due to the long-term suppression of immune system by immunosuppressants used to reduce transplant rejection or regrowth of the remaining undetected tumor cells. Over the years, different immunosuppressive drugs have been introduced for liver transplantation in liver cancer patients [7]. Mammalian target of rapamycin complex (mTORC)1 inhibitors are among the most impressive drugs due to their potent immunosuppressive and anti-oncogenic effects. Earlier studies reported that mTORC1 inhibitors reduced tumor recurrence in HCC patients post liver transplantation compared with conventional calcineurin inhibitors. Nevertheless, a large phase 3 trial (SILVER) showed that although the effect of mTORC1 inhibitors is most beneficial 3 - 5 years post transplantation, recurrence is inevitable after 5 years [8]. One critique of this trial is the heterogeneity of protocols to manage immunosuppression utilized by different participating centers. Nonetheless, there exist recurrent HCC cells resistant to mTORC1 inhibitors.

Drug-resistant HCC cells are commonly identified with the cell surface markers cluster-of-differentiation (CD)13, CD90, CD133, CD44 and epithelial cellular adhesion molecule (EpCAM) [9]. These cells are considered cancer stem cells or tumor-initiating cells (TICs) since they appear during liver cancer-initiating events such as DNA damage, or after therapy with hepatotoxic agents or liver cancer drug treatments. Diethylnitrosamine (DEN) is a commonly-used carcinogen that promotes liver cancer in experimental rodent models by damaging DNA. DEN induced CD133+ and CD44+ liver tumor initiating cells (TICs) experimental mouse livers [5,10]. Liver toxicity caused by alcohol and hepatitis virus proteins induced CD133+ liver TICs in experimental mouse models [11,12]. Multiple TIC markers were induced in tumors resistant to sorafenib, a drug approved for liver cancer therapy with a slight survival benefits to HCC patients [13]. A single-cell transcriptomic analysis further revealed the heterogeneity of HCC [14]. Therefore, it appears that there are more than one or more TIC markers appeared to cause drug resistance in HCC. Nonetheless, the molecular mechanisms of how these diverse TIC markers appear is unclear. One possibility is the emergence of new clones from mutated regenerating hepatocytes in HCC livers from chronic liver injury.

Current therapeutic options for HCC treatment have the potential of exacerbating HCC tumorigenesis. Even tumor resection triggers hepatocyte regeneration in both normal and diseased livers [15]. After partial hepatectomy, regeneration-induced replicative stress enhanced tumorigenesis in multidrug resistant (mdr)2-/- liver, which is chronically inflamed [16]. Sorafenib, a drug approved for HCC, targets the Raf/MEK/ERK pathway, also essential for hepatocyte regeneration [17]. Formerly, mTORC1 would be a promising drug target of HCC since mTORC1 activation is present in the majority of HCCs. Mice without tuberous sclerosis (TSC)1, a negative regulator of mTORC1, spontaneously develop liver tumors [18]. Yet, when mTORC1 is specifically knocked out in mouse liver, DEN-induced tumorigenesis is enhanced [19]. Protein kinase B or Akt, another promising target of HCC, is also essential for hepatocyte regeneration. Knocking out Akt in mouse liver promotes spontaneous development of liver tumors [20]. Liver injury is also observed in patients treated with pan-Akt inhibitors in clinical trials. Therefore, the treatment of liver cancer patients with Akt inhibitors is not warranted in patients with chronic liver injury [21]. Even recently the approved immune checkpoint inhibitor, nivolumab, also causes liver injury in 20% of patients [22] as hepatotoxicity is a commonly observed adverse effect of immunomodulatory drugs [23]. Therefore, tumor recurrence through nonspecific hepatocyte killing poses an obstacle for current and future regimes of HCC treatments.

## Natural medicine and nurtured medicine are potential combinations for cancer

Nature has provided molecules that help resist cancer development. Plant-derived phytochemicals are natural products with chemo-preventive and anticancer properties. Indeed, most FDA-approved drugs are products of nature or derived from natural products. Among 174 drugs approved by FDA to treat cancer, 136 (78%) are small molecules [24]. 113 of 136 drugs (83%) are either natural products or synthetic compounds derived from the pharmacophores of natural products. Paclitaxel, a drug approved to treat a variety of cancers due to its ability to target cancer cells, is one of the recognized natural products that was developed as an effective anticancer drug. Later, the development of albumin-bound paclitaxel, also known as the trade named Abraxane, facilitates enhanced bioavailability and delivery of paclitaxel to tumor tissues with low toxicity. In other cases, drugs such as sorafenib, ataluren, and vemurafenib were synthesized after screening pharmacophores derived from natural products. These examples highlight the importance of natural products in anticancer drug development. More importantly, molecules derived from nature can be further modified to increase their therapeutic effectiveness.

Prior to proceeding further with this argument, it is necessary to understand some caveats. Herbal extracts contain multiple components of varying known and unknown toxicities that create barriers to taking full advantage of the naturally-derived


How to cite this article: Raymond P W. Flavones as Potential Adjuvants for Therapeutic Treatments of Hepatocellular Carcinoma. Adv Res Gastroentero Hepatol, 2020;15(2): 555907. DOI: 10.19080/ARGH.2020.15.555907

beneficial compounds. These barriers should be addressed by the careful experimental testing of purified compounds. Natural products though generally possessing mild anticancer activities as single agents, can provide additive or synergistic anticancer activities when combined with synthetic compounds. Since the natural compounds, which have been taken by humans in traditional medicine or as dietary supplements for hundreds of years, possess relatively no known toxicity, it is desirable to propose the use of natural medicines together with 'nurtured medicine' (synthetic small molecules, therapeutic antibodies, antibody conjugates, and modified cells). Natural and nurtured medicine could form complementary therapeutic efficacy without added toxicity. In some cases, they could even provide lower toxicity usually associated with nurtured medicine.

## Potential use of flavones in liver cancer therapy

Flavonoids are a large class compounds sharing common basic structure [25] enriched in edible fruits and plants as well as plants traditionally known to possess anti-inflammatory and anti-neoplastic medicinal properties [26]. Flavonoids are classified into at least six categories according to their structure: flavones, anthocynidins, flavan-3-ols, flavonols, flavanones, and isoflavones. These compounds have attracted the interest of the cancer research community due to the results of several epidemiological studies suggesting that flavonoids can lower the incidence of cancer and overall mortality [27-29], although some studies show no effects of dietary intake of flavonoids to cancer incidence [30].

The drawbacks of these compounds include their nonspecific antioxidant activity and low plasma availability, limiting their use as potential cancer therapeutic agents. Their 50% killing concentration, IC50, for cancer cells is ~10 μM. Because flavonoids possess functional hydroxyl groups on their backbones, they are considered as "polyphenols and "antioxidants". The current perception toward compounds with antioxidant properties is that they are nonspecific. Moreover, one of the roadblocks in using antioxidant compounds as anticancer drugs is their rapid metabolism and low bioavailability in plasma. However, recent drug development efforts utilize a type of antioxidant functional group called "Michael acceptor" that target cysteine residues on the target proteins to covalently inactivates the targets [31]. Traditionally, compounds with this moiety are considered unsafe due to potential nonselective activity or unstable due to their highly reactive nature. However, conscientious efforts have led to a new strategy to degrade the target proteins using these electrophilic moiety as "warhead". Successful FDA approved drugs were developed using this approach to covalently inactivate the disease targets [31-34].

Flavones are promising anticancer compounds for liver cancer due to their unique pharmacokinetics in liver. Although flavones affect numerous mechanistic important cancer-promoting pathways, few studies have addressed their selective activity in cancer cells versus normal counterparts. When flavones are tested together with other natural products in killing freshly isolated chronic lymphocytic leukemia (CLL) leukocytes and normal human peripheral blood mononuclear cells (PBMC), the flavones apigenin and tangeretin notably selectively kill CLL leukocytes over normal PBMC [35]. Although these compounds killed CLL cells in the μM range, a very high concentration (>40-50 mM) was needed to kill normal PBMC. Moreover, when these compounds were tested in a cancer cell line with the antioxidant response element (ARE) reporter system, relatively low antioxidant activity was present compared with other known oxidants or antioxidants. In a separate study, baicalein, a flavone enriched in many traditional Asian medicine preparations, selectively killed mouse Tumor Initiating Cells (TICs) without killing normal hepatocytes even at 100 mM [36]. These studies suggest that selective anticancer activity would be one attractive property of flavones for further development as anticancer drugs.

The interest in baicalein for the treatment of liver disease owes to its being a major component of traditional oriental herbal medicine long thought to protect the liver. Baicalein is present in many oriental herbal extract preparations, most notably chinese skullcap (Scutellaria baicalensis Georgi) and Scutellariae radix (root of Scutellaria baicalensis). Although there is no clinical evidence reporting the benefits of using baicalein in liver diseases, high intake of baicalein is not associated with significant human toxicity [37,38]. Furthermore, Yan Gan Wan (YGW), a chinese medicine extract containing baicalein was nontoxic to mice fed with YGW for over a year [36]. Moreover, when these mice were challenged with DEN, liver cancer was prevented in mice fed with the diet containing YGW. When mice are fed with YGW, baicalein is accumulated in liver. These data suggest that baicalein can impair liver cancer formation without causing any toxicity. Furthermore, baicalein can protect liver from known hepatoxic chemicals [39-40]. The dual anti-oncogenic and liver protective properties of baicalein warrant further study addressing its use as a potential adjuvant in the treatment of liver cancer.

Other flavones that show dual liver protection and anti-cancer activities include Apigenin and Luteolin. Both Apigenin and Luteolin are found in fruits and vegetables such as parsley, celery and chamomile. Both showed hepatoprotective effects against several known liver damaging chemicals, diet and alcohol in mouse models.

## Summary

Although it is well established that hepatocyte death precedes HCC development, liver toxicity caused by current anti-HCC treatments have been largely ignored. This perspective points to this potential challenge and proposes new therapeutic strategies that selectively promote cancer cell death without affecting the viability of hepatocytes. Therefore, molecules that kill tumor cells without killing normal hepatocytes would be attractive adjuvants for HCC treatment. Baicalein is a flavone with both anti-oncogenic and liver protective property that kill liver TICs resistant to


How to cite this article: Raymond P W. Flavones as Potential Adjuvants for Therapeutic Treatments of Hepatocellular Carcinoma. Adv Res Gastroentero Hepatol, 2020;15(2): 555907. DOI: 10.19080/ARGH.2020.15.555907

mTORC1 inhibition, sparing normal hepatocytes. Therefore, baicalein should be considered as an attractive adjuvant for anti-HCC treatments future clinical studies.

## Acknowledgments

The author would like to thank Dr. Hidekazu Tsukamoto and Dr. Jonathan Kaunitz for helpful comments.

## Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

## References

1. Siegel RL, Miller KD, Jemal A (2019) Cancer statistics, 2019. CA Cancer J Clin 69(1): 7-34.
2. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, et al. (2017) Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. J Natl Cancer Inst 109.
3. Wu J, Yang S, Xu K, Ding C, Zhou Y, et al. (2018) Patterns and Trends of Liver Cancer Incidence Rates in Eastern and Southeastern Asian Countries (1983-2007) and Predictions to 2030. Gastroenterology 154(6): 1719-1728.e1715.
4. Schwabe RF, Luedde T (2018) Apoptosis and necroptosis in the liver: a matter of life and death. Nat Rev Gastroenterol Hepatol 15(12): 738-752.
5. Mu X, Español-Suñer R, Mederacke I, Affò S, Manco R, et al. (2015) Hepatocellular carcinoma originates from hepatocytes and not from the progenitor/biliary compartment. J Clin Invest 125(10): 3891-3903.
6. Boege Y, Malehmir M, Healy ME, Bettermann K, Lorentzen A, et al. (2017) A Dual Role of Caspase-8 in Triggering and Sensing Proliferation-Associated DNA Damage, a Key Determinant of Liver Cancer Development. Cancer Cell 32: 342-359.e310.
7. Lerut J, Iesari S, Foguenne M, Lai Q (2017) Hepatocellular cancer and recurrence after liver transplantation: what about the impact of immunosuppression? Transl Gastroenterol Hepatol 2: 80.
8. Geissler EK, Schnitzbauer AA, Zülke C, Lamby PE, Proneth A, et al. (2016) Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomized, Multicenter, Open-Label Phase 3 Trial. Transplantation 100(1): 116-125.
9. Ma YC, Yang JY, Yan LN (2013) Relevant markers of cancer stem cells indicate a poor prognosis in hepatocellular carcinoma patients: a meta-analysis. Eur J Gastroenterol Hepatol 25(9): 1007-1016.
10. Dhar D, Antonucci L, Nakagawa H, Kim JY, Glitzner E, et al. (2018) Liver Cancer Initiation Requires p53 Inhibition by CD44-Enhanced Growth Factor Signaling. Cancer Cell 33(6): 1061-1077.e1066.
11. Machida K, Tsukamoto H, Mkrtchyan H, Duan L, Dynnyk A, et al. (2009) Toll-like receptor 4 mediates synergism between alcohol and HCV in hepatic oncogenesis involving stem cell marker Nanog. Proc Natl Acad Sci U S A 106(5): 1548-1553.
12. Chen CL, Tsukamoto H, Liu JC, Kashiwabara C, Feldman D, et al. (2013) Reciprocal regulation by TLR4 and TGF-β in tumor-initiating stem-like cells. J Clin Invest 123: 2832-2849.
13. Tovar V, Cornella H, Moeini A, Vidal S, Hoshida Y, et al. (2017) Tumour initiating cells and IGF/FGF signalling contribute to sorafenib resistance in hepatocellular carcinoma. Gut 66(3): 530-540.
14. Zheng H, Pomyen Y, Hernandez MO, Li C, Livak F, et al. (2018) Single-cell analysis reveals cancer stem cell heterogeneity in hepatocellular carcinoma. Hepatology 68(1): 127-140.
15. Nagasue N, Yukaya H, Ogawa Y, Kohno H, Nakamura T (1987) Human liver regeneration after major hepatic resection. A study of normal liver and livers with chronic hepatitis and cirrhosis. Ann Surg 206: 30-39.
16. Barash H, R Gross E, Edrei Y, Ella E, Israel A, et al. (2010) Accelerated carcinogenesis following liver regeneration is associated with chronic inflammation-induced double-strand DNA breaks. Proc Natl Acad Sci U S A 107(5): 2207-2212.
17. Guégan JP, Frémin C, Baffet G (2012) The MAPK MEK1/2-ERK1/2 Pathway and Its Implication in Hepatocyte Cell Cycle Control. Int J Hepatol 2012: 328372.
18. Menon S, Yecies JL, Zhang HH, Howell JJ, Nicholatos J, et al. (2012) Chronic activation of mTOR complex 1 is sufficient to cause hepatocellular carcinoma in mice. Sci Signal 5(217): ra24.
19. Umemura A, Park EJ, Taniguchi K, Lee JH, Shalapour S, et al. (2014) Liver damage, inflammation, and enhanced tumorigenesis after persistent mTORC1 inhibition. Cell Metab 20(1): 133-144.
20. Wang Q, Yu WN, Chen X, Peng XD, Jeon SM, et al. (2016) Spontaneous Hepatocellular Carcinoma after the Combined Deletion of Akt Isoforms. Cancer Cell 29(4): 523-535.
21. Wang Q, Chen X, Hay N (2017) Akt as a target for cancer therapy: more is not always better (lessons from studies in mice). Br J Cancer 117(2): 159-163.
22. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, et al. (2017) Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 389(10088): 2492-2502.
23. Suzman DL, Pelosof L, Rosenberg A, Avigan MI (2018) Hepatotoxicity of immune checkpoint inhibitors: An evolving picture of risk associated with a vital class of immunotherapy agents. Liver Int 38(6): 976-987.
24. Newman DJ, Cragg GM (2016) Natural Products as Sources of New Drugs from 1981 to 2014. J Nat Prod 79(3): 629-661.
25. Kumar S, Pandey AK (2013) Chemistry and biological activities of flavonoids: an overview. Scientific World Journal 2013: 162750.
26. Birt DF, Hendrich S, Wang W (2001) Dietary agents in cancer prevention: flavonoids and isoflavonoids. Pharmacol Ther 90: 157-177.
27. Hui C, Qi X, Qianyong Z, Xiaoli P, Jundong Z, et al. (2013) Flavonoids, flavonoid subclasses and breast cancer risk: a meta-analysis of epidemiologic studies. PLoS One 8(1): e54318.
28. Graf BA, Milbury PE, Blumberg JB (2005) Flavonols, flavones, flavanones, and human health: epidemiological evidence. J Med Food 8(3): 281-290.
29. Grosso G, Micek A, Godos J, Pajak A, Sciacca S, et al. (2017) Dietary Flavonoid and Lignan Intake and Mortality in Prospective Cohort Studies: Systematic Review and Dose-Response Meta-Analysis. Am J Epidemiol 185(12): 1304-1316.
30. Zamora-Ros R, Barupal DK, Rothwell JA, Jenab M, Fedirko V, et al. (2017) Dietary flavonoid intake and colorectal cancer risk in the European prospective investigation into cancer and nutrition (EPIC) cohort. Int J Cancer 140(8): 1836-1844.
31. Schwartz PA, Kuzmic P, Solowiej J, Bergqvist S, Bolanos B, et al. (2014) Covalent EGFR inhibitor analysis reveals importance of reversible interactions to potency and mechanisms of drug resistance. Proc Natl Acad Sci U S A 111(1): 173-178.


**How to cite this article:** Raymond P W. Flavones as Potential Adjuvants for Therapeutic Treatments of Hepatocellular Carcinoma. Adv Res Gastroentero Hepatol, 2020;15(2): 555907. DOI: 10.19080/ARGH.2020.15.555907

32. Hallin J, Engstrom LD, Hargis L, Calinisan A, Aranda R, et al. (2019) The KRAS $^{G12C}$ Inhibitor MRTX8$_{49}$ Provides Insight Toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients. Cancer Discov 10(1): 54-71.

33. Jackson PA, Widen JC, Harki DA, Brummond KM (2017) Covalent Modifiers: A Chemical Perspective on the Reactivity of α,β-Unsaturated Carbonyls with Thiols via Hetero-Michael Addition Reactions. J Med Chem 60(3): 839-885.

34. Canon J, Rex K, Saiki AY, Mohr C, Cooke K, et al. (2019) The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature 575(7781): 217-223.

35. Wu RP, Hayashi T, Cottam HB, Jin G, Yao S, et al. (2010) Nrf2 responses and the therapeutic selectivity of electrophilic compounds in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A 107(16): 7479-7484.

36. Wu R, Murali R, Kabe Y, French SW, Chiang YM, et al. (2018) Baicalein Targets GTPase-Mediated Autophagy to Eliminate Liver Tumor-Initiating Stem Cell-Like Cells Resistant to mTORC1 Inhibition. Hepatology 68(5): 1726-1740.

37. Pang H, Xue W, Shi A, Li M, Li Y, et al. (2016) Multiple-Ascending-Dose Pharmacokinetics and Safety Evaluation of Baicalein Chewable Tablets in Healthy Chinese Volunteers. Clin Drug Investig 36(9): 713-724.

38. Li M, Shi A, Pang H, Xue W, Li Y, et al. (2014) Safety, tolerability, and pharmacokinetics of a single ascending dose of baicalein chewable tablets in healthy subjects. J Ethnopharmacol 156: 210-215.

39. Hwang JM, Tseng TH, Tsai YY, Lee HJ, Chou FP, et al. (2005) Protective effects of baicalein on tert-butyl hydroperoxide-induced hepatic toxicity in rat hepatocytes. J Biomed Sci 12(2): 389-397.

40. Huang HL, Wang YJ, Zhang QY, Liu B, Wang FY, et al. (2012) Hepatoprotective effects of baicalein against $CCl_4$-induced acute liver injury in mice. World J Gastroenterol 18(45): 6605-6613.



**DOI:**10.19080/ARGH.2020.15.555907




**How to cite this article:** Raymond P W. Flavones as Potential Adjuvants for Therapeutic Treatments of Hepatocellular Carcinoma. Adv Res Gastroentero Hepatol, 2020;15(2): 555907. DOI: 10.19080/ARGH.2020.15.555907