POSSIBLE TREATMENT APPROACHES FOR HEPATOCELLULAR CARCINOMA

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Research Paper

Received: **05.05.2021**

Revised: **18.05.2021**

Accepted: **31.05.2021**

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common liver malignancy worldwide. HCC patients are diagnosed in advanced stages, due to its poor prognosis. Currently, immunotherapy and chemotherapy are the best treatment options in >90 cases of liver cancer. Therefore, new treatment options are urgently needed for the cure of liver cancer. Use of nanotechnology and/or some natural compounds may become better options for liver cancer patients with minimum side effects and lower toxicity. This review focuses on present available treatment approaches for the management of liver cancer in patients.

Keywords: Hepatocellular carcinoma, sorafenib, natural agents, immunotherapy, chemotherapy, nanotechnology.

INTRODUCTION

Hepatocellular carcinoma is the most common liver disease and major cause of cancer related death worldwide. Risk factors for HCC include chronic liver disease, cirrhosis, virus infections (hepatitis C and hepatitis B virus), alcohol, diabetes, obesity, iron- overload, smoking and other dietary factors. (Center and Jemal, 2011; Masroor *et al.*, 2020). Due to poor prognosis of HCC, only 5 to 20 percent patients are eligible for surgical treatment. Surgical removal is suitable for early stage liver cancer patients. For advanced stage HCC patients treatment approaches are the following: (i) trans-arterial chemoembolization (TACE) (only 23 percent improvement and increase in 2 years survival rate) for intermediate stage liver cancer patients. (ii) Oral administration of sorafenib, (a kinase inhibitor) that is the best treatment option for late-stage of HCC. However, drug resistance is reported (within 6 months) and only one-third of patients can be cure with this drug (El-Serag *et al.*, 2008). Sorafenib and other chemotherapeutic drugs, have adverse side effects (toxicity and inefficacy of drug) in

liver cancer patients after long- term treatment. Therefore, neither surgical therapies nor chemotherapy is effective for the treatment of this devastating liver disease. To find better treatment options for HCC further research is needed. Our diet play very crucial role in development, progression, prevention and treatment of HCC. A study reported that a higher dietary intake of vegetables and fruits decreases the risk of tumor development (Soerjomataram *et al.*, 2010). Several natural compounds of vegetables, fruits and spices suppress mechanisms that are responsible for cancers development, and they also help in the prevention of this devastating disease. Natural compounds have anti-tumor, anti-inflammatory, immunomodulatory, anti-proliferative and anti-oxidant properties that provide better treatment option for any cancer (Banerjee *et al.*, 2017; Singh *et al.*, 2017; Li *et al.*, 2019; Saha *et al.*, 2020). Piperine is a natural compound that kills only tumor cells without affecting other non cancerous cells (Zhou *et al.*, 2016). It inhibits the activity of enzymes responsible for metabolism of drugs (Bhardwaj *et al.*, 2002). Many other natural compounds are also reported for their anti- cancerous properties. They can

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enhance the efficacy of anti-cancer drugs without causing any kind of toxicity in HCC patients. Our immune system plays an important role in destroying tumor cells. For the prevention of tumor progression biomarkers of uncontrolled growth can be targeted (Chen et al., 2014). A serious drawback of chemotherapeutic agents is multidrug resistance. Cancer stem cells and /or cancer cells are responsible for drug resistance. They initiate pathway for tumor development and metastasis. Immunotherapy is a good treatment approach for liver cancer (Pan et al., 2015). Some other approaches, through cancer vaccines and checkpoint inhibitors of immune system, (eg. PD-1 and PD-L1 targeting), inhibit tumor progression and destroy tumor cells. Sorafenib helps in immunosuppression, therefore can be used for combination therapy (Kudo et al., 2016; Zhao et al., 2015). Recently, nanotechnology can be a possible treatment approach for the better cure of neoplasms by targeting and destroying cancer cells. Nanotechnology is accomplished by standardizing surface properties and size of the drugs for targeting tumor cells with no adverse effects and low systemic toxicity (Reddy et al., 2011). Current combination therapy approaches can be changed by using nanotechnology for the improvement of pharmacokinetic profile retention, permeability and reduction of side effects (Singh et al., 2017; Davis et al., 2008). For the improvement of efficacy of drugs, nanoparticle techniques may provide promising results in liver cancer (Singh et al., 2018; Livney, and Assaraf, 2013). The late diagnosis of HCC leads physicians and scientists to search new treatment approaches for the improvement of survival rate of cancer patients. An alteration in drug delivery system and new combination therapy approaches may give new outcomes for the management of this devastating liver malignancy. In this review, we discuss some of the most common possible approaches including natural agents, immunotherapies, chemotherapies and nanoparticles for the treatment of advanced hepatocellular carcinoma.

Hepatocellular carcinoma: development and progression

HCC is generally characterized by hepatocellular injury/death, inflammation followed by liver fibrosis and cirrhosis. Initially, these damages are reversible. However, if the injury is persistent for long time, liver chronic diseases (alcoholic fatty liver diseases, viral hepatitis and haemochromatosis) may progress to last-

Figure 1: Development and progression of hepatocellular carcinoma (HCC).

stage medical complications (e.g. cirrhosis and HCC) (Fig. 1).

Natural compounds for treatment of HCC

Several natural compounds have reported for the management of liver cancer. Piperine (an alkaloid extracted from long and black peppers) has anti-mutagenic, anti-tumor, anti-proliferative and antioxidant activities (Tawani et al., 2016). It inhibits activity of enzymes (UDP glucuronyl transferase and aryl hydrocarbon hydroxylase) during drug metabolism and decreases lipid peroxidation, results into increase in bioavailability of phytochemicals and drugs (Srinivasan, 2007). It helps in intestinal absorption by interacting with the lipid molecules of the gut (Johri et al., 1992). Drug resistance is a very common problem for many drugs of liver cancer treatment. Otherwise these drugs could be very effective treatment approach for liver cancer. Piperine has no side effect on normal hepatocyte cells of liver. Moreover, this alkaloid increases the activity of caspase-3 and caspase-9 and inhibits catalase, resulting to mitochondria-mediated programmed cell death.

Curcumin (constituent of turmeric) has many biological functions in many diseases, including HCC (Gupta et al., 2013). Curcumin increased the function of piperine on diethylnitrosamine-induced liver cancer in rats. A phenolic compound (Oleocanthal) of olive oil (extra-virgin) stimulates programmed cell death and kills tumor cells (Polini et al., 2018). Additionally, chronic inflammation may develop liver fibrosis, cirrhosis, and end-stage HCC (Bishayee, 2014). COX-2 up-regulation is reported in HCC cells as compared to normal cells and at higher concentrations cancer cells differentiated (Koga et al.,

1999). Oleocanthal has immunomodulatory and anti-inflammatory functions by COX-1 and COX-2 inhibition. It blocked metastasis of HCC by reducing migration and invasion of HCC cell *in vivo*. This natural compound reduced the nuclear translocation of many transcription factor/genes responsible for metastasis (Pei et al., 2016). Another natural compound, allium also have cancer-inhibiting functions and are related with reduced risk of many other cancers (Petrovic et al., 2018). The different flavanols and organosulfur agents of allium extracts block different stages of cancer (Khazaei et al., 2017). Diallyl sulfide and S-allyl cysteine (SAC) (constituents of allium extract) have shown anti-proliferative functions and inhibited diethylnitrosamine-induced HCC (Sengupta et al., 2004). Methanolic extracts of allium demonstrated G0/G1 blockade in liver cancer cells (HepG2) and increased apoptosis. Allium extract with combination of doxorubicin drug is commonly used for chemotherapy in HCC patients. *Viscum album var* (VAV) is used as an herbal drug for chronic liver diseases. Thus, natural plants and their compounds are promising for treatment of HCC.

Chemotherapy for treatment of HCC

Several clinical trial reports suggested that sorafenib (a multi-kinase inhibitor) can be used for the treatment of late stages of HCC patients (Jelic and Sotiropoulos 2010; Kane et al., 2009). Oral administration of sorafenib induces apoptosis of tumor cells by inhibiting cascade of MAP kinase and reduces cell division, proliferation and angiogenesis of tumor. Sorafenib is a FDA approved drug (2007). It increases survival rate (three to five months) of HCC patients as compared to untreated patients (Bruix et al., 2012; Cheng et al., 2009). Long term use of this medicine is not effective because cancer become resistant to this drug. Furthermore, its administration causes side effects in HCC patients. An increase in serum concentration of amylase and lipase, hemorrhage, leukopenia, hypertension, vomiting, diarrhea, nausea and carcinomas have been reported (Anwanwan et al., 2020; Zhu et al., 2017). Sorafenib with chemoembolization is a new and better treatment approach for HCC (Choi et al., 2017). The combination of doxorubicin with sorafenib could be better treatment option for HCC due to their synergistic effect. Another drug tivozanib, known for the treatment of breast, renal and other cancers has limited

reports for/on HCC. Tivozanib inhibits angiogenesis by suppressing VEGF receptor—1 and 2 in colorectal cancers and other cancers (Jamil et al; 2015). Liver cancer stem cells play important role in the development of chemoresistance and growth of tumor due to higher rate of cell survival in HCC (Huo et al., 2017). In HCC patients, combination of cisplatin and 5-FU used for chemotherapies and increased 14 months survival as compared to single drug treated patients (Nouso et al., 2013).

Immunotherapy for treatment of HCC

Immunotherapy is another treatment option for liver cancer patients. In this approach immune system can be modified by blocking the checkpoints of signaling responsible for immunosuppression. To prevent inflammatory response and infection specific vaccines and immunotherapies can be used. These therapies may boost immune system of liver cancer patients. Immunotherapy can give synergistic effect with currently used drugs for the treatment of liver cancer patients (Zhao et al., 2015). In combination therapeutic approach of immunotherapy and chemotherapy, monoclonal antibodies (Bevacizumab, and ramucirumab) are under clinical trial for the treatment of liver cancer (Morse et., 2019). Programmed cell death 1 ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) are checkpoints of immune system (Ho et al., 2019). PD-L1 is expressed in nonimmune cells as well as on T-cells, B-cells, macrophages, dendritic cells, myeloid-derived suppressor cells, antigen-presenting cells, and tumor cells. A protein (PD-1) is expressed on active B-cells, CD4+ and CD8+ T-cells, natural killer cells, Treg cells, monocytes, myeloid cells, and dendritic cells (Greten et al., 2017; Gao et al., 2009). T-cell activity is suppressed by interaction of PD-1 protein and PD-L1 which decreases secretion of some cytokines, interleukin-2 and IFN- γ and inhibit immune signal. Therefore, HCC patients develop anti-cancerous response as well as survival rate of cancer cells also decreases (Gao et al., 2009).

In HCC, PD-L1 can be used as a biomarker due to its association with cancer aggression and recurrence in patients. The combination of sorafenib and anti-PD-1 causes immunosuppression and reduces metastasis and tumor growth in HCC patients (Zhao et al., 2015). PD-1 /PD- L1 blockade reduces other risk factors of HCC (hepatitis C and hepatitis B). Nivolumab (PD-1 inhibitor) is a FDA approved drug.

For HCC patients, nivolumab is a promising treatment option.

Nanotechnology based approaches for treatment of HCC

Recently, nanotechnology based treatment approaches has improved the efficacy of drugs for treatment of HCC. In this approach, scientists are using different nano carrier-based drug delivery systems for the treatment of liver cancer cells. It has less systemic toxicity. An *in vitro* study utilized luminescent, organic dye-doped, core-shell nanoparticles that leach minimally and are photostable to bind covalently with anti-human liver cancer mAbs. An *in vitro* study reported that fluorescent silica nanoparticles effectively seek out liver cancer cell (HepG2) (He et., 2004). This treatment option is very useful for well know chemotherapeutic drug. Several investigators have taken advantage of these techniques to demonstrate improved outcomes in treating liver cancers (Ballout et al., 2018; Xia et al., 2017). Silica with a mesoporous and rattle-type structure was loaded with docetaxel to measure its effectiveness for killing HepG2 cells and for treating mice. This therapy showed very low systematic toxicity and high anti-tumor activity (Li et al., 2010). A lipid-based nanoparticles (MTLCEBPA), restores transcription by targeting the CCAAT enhancer binding protein alpha (CEBPA) gene; which is tumor suppressor gene and results into inhibition of metastasis, cellular proliferation and liver cell function. The gene is down regulated in hepatic cancer cells. The mRNA and protein expression levels are increased due to upregulation of CEBPA gene resulting in to decrease in proliferation of tumor cells. It increases albumin levels and prevents liver failure. Several therapeutic approaches are associated for the treatment of liver cancer by decreasing function of liver.

Conclusion and future prospective

Liver cancer is the most common and fatal malignancy. New drugs and new therapeutic techniques are providing better treatment approach for HCC patients. Now days many treatment approaches are available, including, chemotherapeutics, natural compounds, immunotherapies, and new drug delivery methods for liver cancer. Combination therapy improves the efficacy of available agents. This review provides an overview of current treatment approaches for liver cancer. Although new combination therapy could be beneficial for HCC treatment but to find an ideal

combination of the drugs is still challenge for physicians and scientists. Since the HCC cases and death rates are increasing, scientists / physicians should continue to work on the possible treatment options for the management of HCC.

REFERENCES

1. **Anwanwan D. , Singh S.K., Singh S. Varma S. and Singh R.** (2020). Challenges in liver cancer and possible treatment approaches. *Biochim Biophys Acta Rev Cancer*. 1873 (1): 188314
2. **Ballout F., Habli Z., Rahal O.N., Fatfat M. and Gali-Muhtasib H.** (2018). Thymoquinone-based nanotechnology for cancer therapy: promises and challenges, *Drug Discov Today*. 23: 1089-1098.
3. **Banerjee S., Singh S.K., Chowdhury I., Lillard J.W. and Singh Jr. R.** (2017). Combinatorial effect of curcumin with docetaxel modulates apoptotic and cell survival molecules in prostate cancer. *Front Biosci (Elite Ed)* 9: 235-245.
4. **Bhardwaj R.K., Glaeser H., Becquemont L., Klotz U., Gupta S.K. and Fromm M.F.** (2002). Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. *J Pharmacol Exp Ther*. 302: 645-650.
5. **Bishayee A.** (2014). The role of inflammation and liver cancer. *Adv Exp Med Biol*. 816: 401-435.
6. **Bruix J., Raoul J.L., Sherman M., Mazzaferro V., Bolondi L., Craxi A., Galle P.R., Santoro A., Beaugrand M., Sangiovanni A., Porta C., Gerken G., Marrero J.A., Nadel A., Shan M., Moscovici M., Voliotis D., Llovet, J.M.** (2012). Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol*. 57: 821-829.
7. **Center M.M. and Jemal A.** (2011). International trends in liver cancer incidence rates. *Cancer Epidemiol Biomarkers Prev*. 20: 2362-2368.
8. **Chen, Y., Huang, Y., Reiberger, T., Duyverman, A.M., Huang P., Samuel R., Hiddingh L., Roberge S., Koppel C., Lauwers G.Y., Zhu A.X., Jain R.K. and Duda D.G.** (2014). Differential effects of sorafenib on liver versus tumor fibrosis mediated by stromal-derived factor 1 alpha/C-X-C receptor type 4 axis and myeloid differentiation antigen-positive myeloid cell infiltration in mice. *Hepatology* (Baltimore, Md.) 59: 1435-1447.

9. **Cheng A.L., Kang Y.K., Chen Z., Tsao C.J., Qin S., Kim J.S., Luo R. Feng J., Ye S., Yang T.S., Xu J., Sun Y., Liang H., Liu J., Wang J., Tak W.Y., Pan H., Burock K., Zou J., Voliotis D. and Guan Z.** (2009). Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 10: 25-34.
10. **Choi G.H., Shim J.H., Kim M.J., Ryu M.H., Ryoo B.Y., Kang Y.K., Shin Y.M., Kim K.M., Lim Y.S. and Lee H.C.** (2013). Sorafenib alone versus sorafenib combined with transarterial chemoembolization for advanced-stage hepatocellular carcinoma: results of propensity score analyses. *Radiology.* 269: 603-611.
11. **Davis M.E., Chen Z.G., Shin D.M.** (2008). Nanoparticle therapeutics: an emerging treatment modality for cancer. *Nat Rev Drug Discov.* 7: 771-782.
12. **El-Serag H.B., Marrero J.A., Rudolph, L. and Reddy K.R.** (2008). Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology.* 134: 1752-1763.
13. **Gao Q. Wang X.Y., Qiu S.J., Yamato I., Sho M., Nakajima Y., Zhou J., Li B.Z., Shi Y.H., Xiao Y.S., Xu Y. and Fan J.** (2009). Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clin Cancer Res.* 15: 971-979.
14. **Greten T.F. and Sangro, B.** (2017). Targets for immunotherapy of liver cancer. *J Hepatol.* S0168-8278(17) 32287-0. doi: 10.1016/j.jhep.2017.09.007.
15. **Gupta S.C., Patchva S. and Aggarwal B.B.** (2013). Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J.* 15: 195-218.
16. **He X., Duan, J. Wang K., Tan W., Lin X., and He C.** (2004). A novel fluorescent label based on organic dye-doped silica nanoparticles for HepG liver cancer cell recognition. *J Nanosci Nanotechnol.* 4: 585-589.
17. **Ho C.M., Chen H.L., Hu R.H. and Lee P.H.** (2019). Harnessing immunotherapy for liver recipients with hepatocellular carcinoma: a review from a transplant oncology perspective. *Ther Adv Med Oncol.* 11: 1758835919843463.
18. **Jamil M.O., Hathaway A. and Mehta A.** (2015). Tivozanib: status of development. *Curr Oncol Rep.* 17-24.
19. **Jelic S., and Sotiropoulos G.C.** (2010). Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 21: Suppl 5 v59-64.
20. **Johri R.K., Thusu N., Khajuria A. and Zutshi U.** (1992). Piperine-mediated changes in the permeability of rat intestinal epithelial cells. The status of gamma-glutamyl transpeptidase activity, uptake of amino acids and lipid peroxidation. *Biochem Pharmacol.* 43: 1401-1407.
21. **Kane R.C., Farrell A.T., Madabushi R., Booth B. Chattopadhyay S., Sridhara R., Justice R. and Pazdur R.** (2009). Sorafenib for the treatment of unresectable hepatocellular carcinoma. *Oncologist.* 14: 95-100.
22. **Khazaei S., Esa N.M., Ramachandran V., Hamid R.A., Pandurangan, A.K., Etemad A. and Ismail, P.** (2017). In vitro Antiproliferative and Apoptosis Inducing Effect of Allium atroviolaceum Bulb Extract on Breast, Cervical, and Liver Cancer Cells. *Front Pharmacol.* 8: 5.
23. **Koga H., Sakisaka, S., Ohishi M., Kawaguchi T., Taniguchi E., Sasatomi K., Harada M., Kusaba T., Tanaka M., Kimura R., Nakashima Y., Nakashima O., Kojiro M., Kurohiji T. and Sata M.** (1999). Expression of cyclooxygenase-2 in human hepatocellular carcinoma: relevance to tumor dedifferentiation. *Hepatology* (Baltimore, Md.) 29: 688-696.
24. **Kudo, M.** (2016). Immune Checkpoint Blockade in Hepatocellular Carcinoma: 2017 Update. *Liver Cancer.* 6: 1-12.
25. **Li L., Tang F., Liu H., Liu T., Hao N., Chen D., Teng X. and He J.** (2010). In vivo delivery of silica nanorattle encapsulated docetaxel for liver cancer therapy with low toxicity and high efficacy. *ACS Nano.* 4(11): 6874-6882.
26. **Li X., Sun R. and Liu, R.** (2019). Natural products in licorice for the therapy of liver diseases: Progress and future opportunities. *Pharmacol Res.* 144: 210-226.
27. **Livney, Y.D. and Assaraf, Y.G.** (2013). Rationally designed nanovehicles to overcome cancer chemoresistance. *Adv Drug Deliv Rev.* 65: 1716-1730.

28. **Masroor M.S., Parween S., Salim M. and Prajapati I.P.** (2020). A Note on Hepatitis Viruses causing Cancer in Human. *International Journal of Biological Innovations*. 2 (2): 126-128. <https://doi.org/10.46505/IJBI.2020.2207>.
29. **Morse M.A., Sun W., Kim R., He A.R., Abada P.B., Mynderse M. and Finn R.S.** (2019). The Role of Angiogenesis in Hepatocellular Carcinoma. *Clin Cancer Res*. 25: 912-920.
30. **Nouso K., Miyahara K., Uchida D., Kuwaki K., Izumi N., Omata M., Ichida T., Kudo M., Ku Y., Kokudo N., Sakamoto M., Nakashima O., Takayama T., Matsui O., Matsuyama Y. and Yamamoto K. J.** (2013). Liver Cancer Study Group of, Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan. *Br J Cancer*. 109: 1904-1907.
31. **Pan Q.Z., Pan K., Wang Q. J., Weng D.S., Zhao J. J., Zheng H.X., Zhang X.F., Jiang S.S., Lv L., Tang Y., Li Y.Q., He J., Liu Q., Chen C.L., Zhang H.X. and Xia, J.C.** (2015). Annexin A3 as a potential target for immunotherapy of liver cancer stem-like cells. *Stem Cells*. 33: 354-366.
32. **Pei T., Meng Q., Han J., Sun H., Li L., Song R., Sun B., Pan S., Liang D. and Liu L.** (2016) (-) Oleocanthal inhibits growth and metastasis by blocking activation of STAT3 in human hepatocellular carcinoma. *Oncotarget*. 7: 43475-43491.
33. **Petrovic V., Nepal A., Olaisen C., Bachke S., Hira J., Sogaard C.K., Rost L.M., Misund K., Andreassen T., Melo T.M., Bartsova Z., Bruheim P. and Otterlei M.** (2018). Anti-Cancer Potential of Homemade Fresh Garlic Extract Is Related to Increased Endoplasmic Reticulum Stress. *Nutrients*. 10 (4): 450.
34. **Polini B., Digiacomo M., Carpi S., Bertini S., Gado F., Saccomanni G., Macchia M., Nieri P., Manera C. and Fogli S.** (2018). Oleocanthal and oleacein contribute to the in vitro therapeutic potential of extra virgin oil-derived extracts in non-melanoma skin cancer. *Toxicol In Vitro*. 52: 243-250.
35. **Reddy L.H. and Couvreur P.** (2011). Nanotechnology for therapy and imaging of liver diseases. *J Hepatol*. 55: 1461-1466.
36. **Saha D., Vaishnav N., Ahsan Z., Rani N., Mathur R. and Jha A.K.** (2020). Reversal of hypermethylation and reactivation of Tumor Suppressor Genes due to natural compounds in Breast Cancer Cells. *International Journal of Biological Innovations*. 2 (1): 63-75. <https://doi.org/10.46505/IJBI.2020.2109>
37. **Sengupta, A. Ghosh, S. and Bhattacharjee, S.** (2004). Allium vegetables in cancer prevention: an overview. *Asian Pac J Cancer Prev*. 5: 237-245.
38. **Singh S.K., Banerjee S., Acosta E.P., Lillard J.W. and Singh R.** (2017). Resveratrol induces cell cycle arrest and apoptosis with docetaxel in prostate cancer cells via a p53/ p21WAF1/CIP1 and p27KIP1 pathway. *Oncotarget*. 8: 17216-17228.
39. **Singh S.K., Lillard J.W., and Singh R.** (2018). Reversal of drug resistance by planetary ball milled (PBM) nanoparticle loaded with resveratrol and docetaxel in prostate cancer. *Cancer Lett*. 427: 49-62.
40. **Singh S.K., Singh S., Lillard Jr., Singh R.** (2017). Drug delivery approaches for breast cancer. *Int J Nanomedicine*. 12: 6205-6218.
41. **Soerjomataram I., Oomen D., Lemmens V., Oenema A., Benetou V., Trichopoulou A., Coebergh J.W., Barendregt J. and de Vries E.** (2010). Increased consumption of fruit and vegetables and future cancer incidence in selected European countries. *Eur J Cancer*. 46: 2563-2580.
42. **Srinivasan K.** (2007). Black pepper and its pungent principle-piperine: a review of diverse physiological effects. *Crit Rev Food Sci Nutr*. 47: 735-748.
43. **Tawani A., Amanullah A., Mishra A. and Kumar A.** (2016). Evidences for Piperine inhibiting cancer by targeting human G-quadruplex DNA sequences. *Sci Rep*. 6: 39239.
44. **Xia Q., Li L. and Zhao, L.** (2017). Silica nanoparticle-based dual-responsive nanoprodrug system for liver cancer therapy. *Exp Ther Med*. 14: 2071-2077.
45. **Xiaoqi Huo S. H., Wu G., Latchoumanin O., Zhou G. Hebbard L., George J. and Qiao, L.** (2017). Dysregulated long noncoding RNAs

- (lncRNAs) in hepatocellular carcinoma: implications for tumorigenesis, disease progression, and liver cancer stem cells. *Molecular Cancer*.
46. **Yadav N. and Mishra Y.** (2020). Targeting the PI3K/AKT Signaling Pathway in Hepatocellular Carcinoma: Current State and future trends. *In: e-book titled "Recent Advances in Cancer Signal Transduction and Therapy"*, Bentham Science Vol (1): pp. 85-98.
 47. **Zhao X., Chen Q., Liu W., Li Y., Tang H., Liu X. and Yang X.** (2015). Codelivery of doxorubicin and curcumin with lipid nanoparticles results in improved efficacy of chemotherapy in liver cancer. *Int J Nanomedicine*. 10 257-270.
 48. **Zhao X., Chen Q., Liu W., Li Y., Tang H., Liu X. and Yang X.** (2015). Codelivery of doxorubicin and curcumin with lipid nanoparticles results in improved efficacy of chemotherapy in liver cancer. *Int J Nanomedicine*. 10 257-270.
 49. **Zhou Y., Li Y., Zhou T., Zheng J., Li H.B. and Li S.** (2016). Dietary Natural Products for Prevention and Treatment of Liver Cancer. *Nutrients*. 8: 156.
 50. **Zhu Y.J., Zheng B., Wang H.Y., Chen L.** (2017). New knowledge of the mechanisms of sorafenib resistance in liver cancer. *Acta Pharmacol Sin*. 38: 614-622.