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In silico Drug Designing and Phytochemicals prospect in Liver Cancer Therapeutics

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Abstract
Cancer is a major public health problem worldwide. Affecting people of all ages, cancer cuts through society, causing suffering on a global scale. According to the World Health Organization, cancer is responsible for one in six deaths, making it the second most common cause of death globally. Hepatocellular carcinoma (HCC) is the most frequent cause of all liver cancers and constitutes 90% of liver cancers globally. The mortality in HCC is very high; about 7 Lakhs of death due to HCC occur annually and has been estimated to be 3rd common cause of death due to cancers affecting humans. The increasing knowledge of molecular and tumor biology has notably changed cancer treatment paradigms during the past 15 years. Current primary cancer management treatments include surgery, cytotoxic chemotherapy, targeted therapy, radiation therapy, endocrine therapy, and immunotherapy. Despite the endeavors and achievements made in treating cancers during the past decades, resistance to classical chemotherapeutic agents and/or novel targeted drugs continues to be a major problem in cancer therapies. The drug discovery process is very complex and includes an interdisciplinary effort for designing effective and commercially feasible drugs. In pharmaceutical, natural medicine, as well as in other scientific research, computers play a very important role, even in the development of new compounds in the quest for better therapeutic agents. A combination of rational drug design and structural biology leads to the discovery of novel therapeutic agents. For this purpose, the Computer-aided drug design (CADD) Center works with collaboration between structure biologists, biophysicists, and computational scientists for the discovery of new chemical entities. CADD and bioinformatics tools in the field of phytochemicals provide benefits like cost-saving, time to market, in-sight knowledge of drug-receptor interactions, speed up drug discovery and development.

Keywords: *Liver Cancer, CADD, Phytochemicals, Natural medicine, Drug resistance.*

I. Introduction

The term carcinoma was coined by Hippocrates (400BC) Father of medicine, carcinoma is a Greek word referring to the crab, which looks much like the finger of crab, and the Latin word for crab is cancer. By 1700, surgeons were operating on cancers. Cancer is where the uncontrolled proliferation of cells that arise from virtually any type of cell in the body. Cancer is also a global disease as each year, almost around ten million cancer patients are diagnosed around. It is the second most common leading cause of death around the world (Blackadar,2016). Among all types of cancer, Liver cancer is one of the most challenging diseases. The liver can be considered as the powerhouse of the body, involved in regulating different body functions when there is an obstruction to the flow of the bile from the liver tumor. Sometimes the inflammation in the liver is seen, which is the symptom of hepatitis, and viral hepatitis is of five types (A, B, C, D, E) in which hepatitis C is the chronic one. Surgery, chemotherapy, and radiotherapy have been used as the treatment of Liver cancer for a very long time (Waldum et al., nd) (Yamashita and Kaneko, 2016). However, Natural compounds can fight against the aggressiveness of Liver cancer, inhibit cancer cell proliferation, and modulate cancer-related pathways. A large number of research works are now focusing on the natural and dietary compounds and trying to find out new and more effective treatment strategies for Liver cancer patients. In this Work, we are exploring some significant natural chemical compounds and interaction with targets related to Liver cancer via the CADD approach, which can be very effective against Liver cancer and can be more potent by their proper modifications and further pre-clinical research. Herbal therapeutics used for the treatment of disease from the long traditions. Herbal medicines are not just a clinical relationship. It's the actual medicines that come from plants, and they can be simple as the plane powder mixes together into a tea and complex as extracting those same plants in various ways and then recombining them into a formula. Future research focusing on the natural anti-Liver-cancer agents can open a new horizon in Liver cancer treatment, which will play a great role in enhancing the survival rate of Liver cancer patients at any stage. Drug design can be done by two methods, either structure-based or ligand-based (Ryerson et al., 2016) (Wu, 1998) (Kapetanovic, 2008).

Here we use the phytochemicals as a ligand, Because for making herbal drugs so we have to find our phytochemicals of herbs. This information of phytochemicals can be taken from online servers available whether Indian server named as IMPPAT(Indian medicinal

plants, Phytochemistry, and therapeutics**) (**https://cb.imsc.res.in/imppat/home) (Mohanraj et al., 2018).Chinese server named (TCMSP) The traditional Chinese medicine systems pharmacology database and analysis platform. TCMSP is Chinese software. All the herbal and plant-related information are easily available (https://www.tcmspw.com/tcmsp.php) (Ru et al., 2014). And other servers also can be used. The treatment of liver cancer is done by different methods some are surgical, and some are non-surgical one of the most preferred method by normal people are chemotherapy or liver transplant. Another name of Herbal medicine or herbal is phytotherapeutic/phytomedicines agents. Herbal medicines can be prepared by the use of more than one herbal substance. Herbal plants or its roots are used for the treatment of cancer, and other diseases are used from ancient time because it is effective in the use and does not have mild side effects. The compounds made from the herbal composites are considered interest among a physician specializing in cancer diagnosis (Liu et al., 2015) (Li et al., n.d)

Computer-aided drug design is the computational approach that makes drug design easy its feature helps to understand the complex biological processes which are used to make biologically active molecules and design and develop new molecules with similar activity. Also, some effects are seen. Sometimes similar molecules have good effects, while sometimes if targeting is not done correctly, it has harmful effects, doses of drugs and its percentage effects are also keep in mind while making any drugs which can be predicted by its pharmacokinetics, toxicity, and other properties. New drugs can be very easily developed by the use of computational methods of drug designing. Drugs are of different kinds molecular, herbal, chemical drugs in which herbal are considered to be the drug with the least side effects. With having the knowledge of its properties of structure which we get from the server named swiss ADME, these properties are pharmacokinetics and pharmacodynamics, blood-brain barrier whether the phytochemical we selected can cross the blood-brain barrier or not if it can cross it can affect our brain and can damage its functions[6], (Yu et al., 2017). The principle behind the CADD is it consists of the use of any software program-based process for establishing a standard relate activity to a structure; it is basically a software program where you will get the activity of the structure or the lead compound or the target we are looking for. CADD approach is done by two methods structure-based and ligand-based drug design. In ligand-based drug design, pharmacophore modeling, or QSAR (quantitative structure-activity relationship). Virtual screening is found to be the most convenient tool now a day to find out the most favorable bioactive compounds with the help of information about the target protein or the known active ligands. Insilco discovery and drug design is the better option for the discovery of new drugs nowadays (Yu et al., 2017) (Aparoy et al., 2012)

II. In Silico Drug Design and Development

The traditional drug development and discovery process is a very complex process that involves years of scientific research and trials, up to 14 years starting from lead identification to clinical trials (Song et al., 2009). On top of the high costs incurred, a significant number of drugs fail to pass the clinical trials due to poor pharmacokinetic properties, insufficient specificity, and side effects (Bohm and Schneider 2000). To solve this problem, Computer-aided drug design (CADD) came into existence which integrated computing power with the practice of medicine and brought about a revolution in the pharmaceutical industry. It provides us with a lot of benefits like low cost, time to market, speeding up the drug discovery process, in-sight knowledge of interactions between drugs and receptors. Virtual Screening refers to the identification of leads or hits through computational methods. It utilizes a detailed database searching approach (commercial, public, or private 3-dimensional chemical structure databases) to find novel drugs for unexplored drug targets or alternatives to already existing drugs (Kapetanovic, 2008). It has been reported that hit rates, i.e., no. of compounds binding to the target divided by total no. of tested compounds, is 2 to 3 times more in virtual screening as compared to empirical screening (Shoichet, 2004). The majority of the methods used in CADD can be divided into two main categories on the basis of the origin of data used – ligand-based drug design and structure-based drug design:

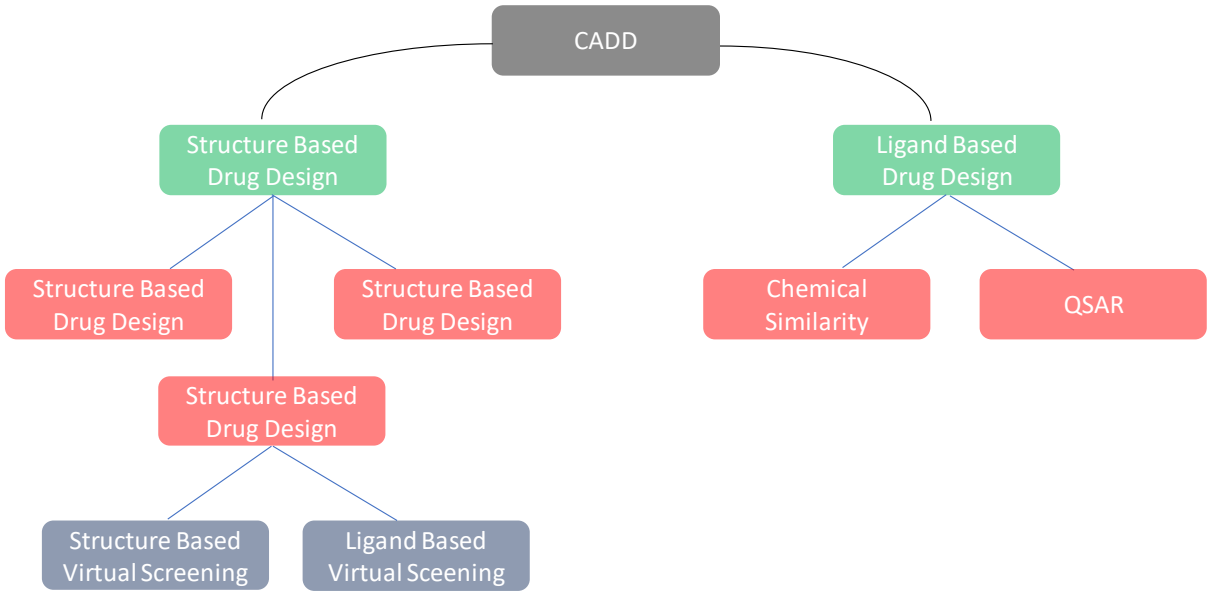

Figure 1: Summary outline showing the various types of computer-aided drug designing.

A. Structure-Based

In this type of drug designing, 3D information of the molecular target should be known. The target is typically a protein or an enzyme involved in a major signaling pathway of the disease. Drugs are designed so as to modify the structure and behavior of the target by either inhibiting or restoring them depending on their role in causing the disease (Anh Vu et al., 2015). This process requires structural information about the receptor, which is collected from X-ray crystallography methods, computationally through homology modeling or NMR (Kapetanovic, 2008). It involves a technique called molecular docking of the potential ligands to the target's binding site. It examines the molecular interactions between the two to identify the efficacy of the drug candidates. It consists of two steps – ligand conformation, orientation and position prediction (pose), and assessing the binding affinity. Multiple conformations and orientations of the ligand are generated and evaluated, and the most efficient ones are selected based on a scoring function that estimates the binding free energy. Knowing about the position of the binding site beforehand significantly enhances the efficiency of molecular docking. These can be obtained by comparing the target with a similar family of proteins having similar functions or with proteins co-crystallized with other ligands (Meng et al., 2012). In case no information is known, there are various online servers and cavity detection programs for performing blind docking like GRID(Kastenholz et al., 2000), POCKET (Levitt & Banaszak, 1992), PASS (Brady & Stouten, 2000), MMC (Mezei, 2003)and SurfNet (Laskowski, 1995). Some of the commonly used docking software are AutoDock, Gold, Pyrex (for multiple ligands), Dock, Insight II Affinity, and Cerius2 LigandFit, Sybyl, and Glide (Kapetanovic, 2008).

B. Ligand Based

These methods are used when there is no information about the 3D structures target protein and focus on active ligands instead of the target protein's structure. For example, G protein-coupled receptors (Rai et al., 2010). In this method, a known set of structurally diverse active compounds are collected to create a receptor model by utilizing the ligand information. These are known as pharmacore models (insert citation pharmacore book). This model can be used for the virtual screening of libraries of compounds to identify potential new binding ligands. Select a query for virtual screening or alignment in ligand-based design (Hamza et al., 2012). It consists of two important steps – an accurate similarity and a scoring measure with sufficient speed.

III. Herbal Therapeutics for liver cancer

Natural compounds present certain advantages. For example, a lot of compounds have been shown to induce tumor-suppressing autophagy, anti-microbial properties, and comparatively lesser side effects. Studies show that bioactive compounds like curcumin and caffeine bring about autophagy in tumor cells (N. Wang & Feng, 2015), and cinnamaldehyde, carvacrol, curcumin, and eugenol have the antimicrobial effect (Ouattara et al., 1997)(Sharma et al., 2014)

A. Lycopene

Lycopene is a naturally occurring chemical found in fruits and vegetables and gives them the 'red' pigmentation. Due to its antioxidant properties, it has shown to be effective for a variety of malignancies, including HCC, by influencing their progression (Mein et al., 2008)(Ip et al., 2013). Studies show it can inhibit cell growth, migration, and invasion in hepatoma cell lines (Jhou et al., 2017). It has also been shown to delay N-nitrosodiethylamine (NDEA) induced hepatocarcinogenesis in rodents (Bhatia et al., 2018). According to a study, lycopene brought down the number, volume, and size of hepatic nodules in rats that had been injected with DEN to induce hepatocarcinogenesis (Sahin et al., 2014). It was found to do that by inhibiting the NF- KB and mTOR pathways.

CYP2E1 has been proved to play a crucial role in the induction of procarcinogens to carcinogens, thereby causing HCC. This has been done through studies involving the chemical inhibition of this enzyme which showed a significant reduction of alcohol-induced hepatocellular adenomas(Stice et al., 2015). Lycopene-rich tomatoes have been shown to reduce the development of Alcoholic fatty liver disease (ALD) by inhibiting CYP2E1. Experiments provide evidence that it promotes the expression of pro-apoptotic genes like p53. Caspase 3,9 and lowers inflammation (Gupta et al., 2013).

B. Phloretin

Phloretin belongs to a class of secondary metabolites called dihydrochalcones and has anti-cancer, antifungal, anti-osteoclastogenic, anti-inflammatory, and antibacterial activities. It also has the ability to increase the penetration of administered drugs (Behzad et al., 2017). It can be extracted from apple leaves and Manchurian Apricot. It has been shown to be effective against liver cancer by showing hepatoprotective effects. In one investigation, effects of phloretin and PIH (phloretin isonicotinyl hydrazone) were analyzed on d-galactosamine (D-GalN)-induced acute liver damage in Kunming mice (Behzad et al., 2017). These compounds were found to significantly reduce the serum ALT, AST, γ-GT, ALP, and TB in acute liver damage and resulted in a decrease in hepatic lesions. They also displayed antioxidant effects on lipid peroxidation in rat liver mitochondria in vitro, and DPPH or ABTS free radical scavenging activity in vitro, and supercoiled pBR322 plasmid DNA. Phloretin has been exhibited to suppress xenograft tumor growth in implanted human cancer cells in athymic nude mice. It arrests the growth of cancer cells by blocking cyclins and CDKs to induce apoptosis by activating mitochondria mediated cell death. The anti-cancer effect is further confirmed by the downregulation of GLUT2 mRNA and proteins which bock the glycolytic pathway and inhibit migration of tumor cells (Lin et al., 2016). In one experiment, APC (adenomatous polyposis) mice were fed a polyphenolic extract obtained from apple for 12 weeks and showed a considerable reduction in the number and size of polyps in the colon and intestine (Fini et al., 2011)In an experiment by (Saraswati et al., 2019), Phloretin sensitivity was tested on 5 HCC cells in which the signal transduction and phosphatase activity were examined. Phloretin was docked with SHP-1, whose structure was downloaded from RCSB PDB (pdb id 3PS5) using autodock vina. Further, Phloretin was docked with AKT1 (4EJN). Binding scores were calculated as per (Hopkins et al., 2014).

It was found to inhibit cell growth and trigger apoptosis in all 5 cells by upregulating the expression of SHP-1, downregulating STAT3 expression, and inhibiting pAKT/pERK signaling.

S.No.	PubChem ID	Source plant	Phytochemical name
1-	969516	Curcuma longa	Curcumin
2-	5280343	Flavanoidobtained from flavonol found in berries, cherries, broccoli, and citrus fruits.	Quercetin
3-	31553	Milk thistle	Silibinin A
4-	3220	Isolated mainly from three sources rhubarb, buckthorn, and Japanese knotweed (Reynoutria japonica syn. Polygonum cuspidatum). It is specifically isolated from Rheum Palmatum L.	Emodin
5-	445154	Found in foods such as peanuts, pistachios, grapes, red and white wine, blueberries, cranberries, and also in cocoa and dark chocolate.	Resveratrol
6-	2353	European barberry, goldenseal, goldthread, greater celandine, Oregon grape, Phellodendron, and tree turmeric	Berberine
7.`	446925	Tomatoes, pink grapefruit, apricots, red oranges, watermelon, rosehips, and guava	Lycopene
8.	4788	Natural dihydrochalcone is found in apple tree leaves and the Manchurian apricot.	Phloretin
9.	2519	Fruit, leaves, and beans of coffee, cacao, and guarana plants	Caffeine
10.	65064	Green and black tea	Epigallocatechin-3-Gallate (EGCG)
11.	5281233	Carotenoid chemical compound found in the flowers crocus and gardenia, responsible for the color of saffron	Crocin
12.	44566638	Potent saponin from Solanum nigrum Linn	Uttroside B

C. Caffeine

Caffeine is a natural compound that acts as a stimulant for the central nervous system (and some parts of the autonomic nervous system) and helps with the alertness of the brain. It belongs to the class of methylxanthene and acts through antagonism of the adenosine receptors (Nehlig et al., 1992). It activates the noradrenaline neurons and affects dopamine release. It can be extracted from coffee beans, various teas, and cacao beans. It is usually used in energy supplements, pain relief products, and cosmetic products. Coffee has been reported to prevent the occurrence of hepatocellular carcinoma. Various models like animals and cell cultures have been used for these studies, one of which indicates that some coffee compounds like kahweol, diterpenes, and cafestol can modulate multiple enzymes involved in carcinogenic detoxification and also modulate the xenotoxic mechanism by inhibiting N-acetyltransferase and inducing glutathione-S-transferase (Muriel & Arauz, 2010). Caffeine, one of the main active compounds present in coffee, has also been shown to inhibit the activation of HSC (Hepatic Stellate cell) in rat models of alcoholic liver fibrosis (Q. Wang et al., 2015). It was found that caffeine significantly reduced liver fibrosis in the ALF rat model by inhibiting cAMP/KA/CREB signaling pathway through adenosine receptors. In one animal study, caffeine levels were found to be inversely proportional to liver injury (He et al., 2001). Another study in the US showed that high consumption of caffeine (in coffee) was linked to a lower rate of liver injury marked by abnormal alanine aminotransferase activity (Ruhl & Everhart, 2005). Some studies report that caffeine induces apoptosis in pancreatic cancer(Gururajanna et al., 1999) and neuroblastoma cells(Jang et al., 2002); however, in HCC, caffeine didn't induce apoptosis and only arrested cell cycle. It was shown to be involved in the activation of the MEK and ERK pathways, which ultimately resulted in the downstream upregulation of EGFR (epidermal growth factor receptor). Interestingly, a cohort study in Japan showed that increased intake of caffeine in the form of coffee, tea, and other sources was not related to liver cancer risk; however, decaf coffee was linked to reduced risk of liver cancer (Tamura et al., 2018).

D. Epigallocatechin-3-Gallate (EGCG)

EGCG is catechin which is a polyphenolic compound found in green tea and is associated with the health benefits ascribed to green tea. It is also present in small amounts in fruits such as kiwis, apples, avocados, and nuts like pecans, pistachios, and hazelnuts. The benefits include anti-cancer effects, antioxidant effects, improving cardiovascular health, protection from radiations to the skin, weight loss, etc. Due to its antioxidant properties, it provides protection against oxidative stress and represses the activity of pro-inflammatory chemicals like TNF-alpha (Tumour necrosis factor-alpha) (Ohishi et al., 2016). It has also been demonstrated to regulate various disease-specific molecular targets, especially cancer. It has been found to be effective against several types of cancer, including HCC, owing to its anti-inflammatory and anti-oxidant properties, which lead to tumor regression (Bimonte et al., 2019). It also acts as a pro-oxidant when presented with an increased concentration of transition metals, which leads to the generation of ROS (Reactive oxygen species), resulting in the DNA breakage of cancer cells (Farhan et al., 2016)(H. Zhang et al., 2010). One report shows that EGCG inhibited the secretion and growth of AFP in human hepatoma-derived PLC/PRF/5 cells without affecting their viability(Nishida et al., 1994). In C3H/HeNCrj mice, it inhibited spontaneous hepatoma without showing any symptoms of toxicity(Takahashi et al., 2010). Useato et al. demonstrated that EGCG could inhibit the growth of HCT116 colorectal and HepG2 HCC cells, but with a lower effect with respect to (-)-epicatechin (Uesato et al., 2001). In vitro studies show that EGCG induced apoptosis in HCCLM6 cells by arresting the cell cycle at G0/G1 phase and by decreasing the mitochondrial membrane potential (Y. Zhang et al., 2013). A reverse docking method was applied to EGCG for identifying potential cancer targets, using reverse docking tools such as TarFisDock, idTarget, INVDOCK, and conventional software like Autodock Vina DOCK, Glide)(W. Wang et al., 2019). Further, MD simulations were applied. The results showed its possible involvement in 12 signal transduction pathways and 33 viral target proteins. 4 novel targets were identified, namely IKBKB, KRAS, WEE1, and NTRK1. Hence these targets and pathways can be utilized for devising therapeutic strategies.

E. Crocin

Crocin is a major biomolecule belonging to the class of glycosylated carotenoids present in the saffron spice and is responsible for its deep red color and unique taste. Chemically, it is a diester formed from the reaction of disaccharide gentiobiose and dicarboxylic acid crocetin. It has traditionally been used as an antioxidant and as Chinese medicine to improve blood circulation (Yao et al., 2018). It has also been shown to have anti-cancer effects by inducing apoptosis and inhibiting tumor proliferation(Hoshyar & Mollaei, 2017) in multiple cancerous cells like gastric carcinoma, head and neck cancer, and HCC. It not only suppresses tumor cell survival in HepG2 cells by targeting different downstream effectors to suppress proliferation but also prevents early liver damage (Noureini & Wink, 2012). In one study, HepG2 and HCCLM3 cell lines were used, and the CCK-8 (Cell counting kit – 8) assay showed that crocin treatment delayed the growth of these cells in a time and dose-dependent manner (Yao et al., 2018). Another investigation reveals that tubulin can be a primary target for crocin for anti-tumor activity(Z. Wang et al., 2020). CRO_E1 was identified to be the most likely binding mode out of 20 different binding modes of crocin in the vinca binding pockets. By using energy decomposition, hot residues for CRO_E1 were identified as Gln^{11}, Gln^{15}, Thr^{72}, Ser^{75}, Pro^{173}-Lys^{174}-Val^{175}-Ser^{176}-Asp^{177}, Tyr^{222}, and Asn^{226} in the β-chain, and Asp^{245}, Ala^{247}-Leu^{248}, Val^{250}, Asn^{329}, and Ile^{332} in the α-chain.

F. Uttroside B

Uttroside B is a saponin derived from the leaves of Solanum nigrum, also called Black nightshade and Manithakkali in Malayam, which grow as unwanted weeds across India. It has been found to show anti-cancer properties and act as a potent cure for liver cancer. It has previously been used as a traditional medicine for jaundice, asthma, skin disorders, and inflammation. When screened for cytotoxicity against 7 cancer cells including skin (A375), liver (HepG2), Colon (HCT -116), Cervical (HeLa), Leukemia (HL60), Breast (MDA-MB-231), lung (A549) through MTT assay, HepG2 cells were affected the most with Uttroside B (Nath et al., 2016). The cytotoxicity of this natural compound was then compared to sorafenib which is the only FDA-approved drug for liver cancer, and it showed 12 fold more efficacy than sorafenib. It was also observed that this compound induced apoptosis in HepG2 cells but didn't affect any phase of the cell cycle. It was also shown to inhibit MAPK and mTOR signaling, as demonstrated by electrophoretic mobility shift assays. In addition to these, a toxicological evaluation suggested that there was no considerable deviation in the WBC and serum levels of AST, ALT, ALP, and BUN in control and Uttroside B treated mice, proving its safety and non – toxicity.

G. Curcumin

Curcumin is a natural phenol, and it is a bright yellow chemical compound obtained from a plant named Curcuma longa. It belongs to the diarylhptenoid (group of curcuminoids). Curcumin works as the active phytoconstituent of turmeric. Curcumin has an anti-oxidant; it works by improving the level of an enzyme called superoxide dismutase. This enzyme plays a very important role in the anti-oxidation mechanism of the body (Panda et al., 2017). Anti-inflammatory, inflammation plays a very important role in disease progression, and curcumin has been shown to be effective in suppressing the various molecular markers of inflammation via suppressing inflammatory chemokine's. Anti-cancer curcumin has been shown to have dose-dependent chemoprotective effects against tumor formation; its anti-cancer property is related to its ability to suppress transcription factors and cellular signaling molecules. Also, it is used as a medicine for many therapeutic in IMPPAT. Antimicrobial effect curcumin is found to be effective against viral, bacterial, and fungal effects. It is also known to enhance the effects of the treatments by strengthening the immune system of the body (Rahmani et al., 2014). Different treatments are used in liver cancer treatment some are surgical like liver transplantation, and other are chemotherapy, radiotherapy, they have side effects like chemotherapy have sometimes adverse side effect while on the other hand, herbal medicines are much safer as compared to chemical medicines with less side effects and cheaper than the other and less toxic as we use curcumin in different medicines because many signaling pathways can be modified and change the cancer pathway into anti-tumor pathways as it is a good adjuvant. LCSCs liver cancer stem cells these cells growth promote cancer, and curcumin affects its growth and can inhibit the growth of cancer cells. Also, a colorimetric assay which is an MTT assay used to assess LCSCs increased in cancer cells and also programmed cell death. PI3K/AKT/mTOR is the signaling pathway used by curcumin to inhibit the growth of LCSCs.Various studies are done, and it is noted that some factors involved in the effect of curcumin in the cancer cells are NF-kB, mitogen-activated protein kinase signaling pathway, Wnt/β-catenin, Notch-1. Curcumin may be an effective phytochemical to inhibit the growth of liver cancer stem cells. Curcumin has been shown to enhance the repair mechanism leading to wound healing and tissue remodeling. In the future, curcumin may be used as adjuvant therapy for liver cancer treatment (Wang et al., 2018).

H. Quercetin

Quercetin belongs to the group of flavonoids found naturally in foods such asred onions, apples, plumbs, red grapes, green tea, elderflower, and onions. It is a natural anti-inflammatory, anti-allergy nutrient. These are strong antioxidants, and the antioxidant is the nutrient that scavenges free radicals and inhibits the oxidation of molecules. Free radicals are unstable atoms that can damage cells and cell membranes. If you are suffering from measurable symptoms of allergy, you may consider Quercetin; several studies have concluded that quercetin can control the growth of hazardous cancerous cells. It fights against free radicals, too, and significantly protects our bodies from them. Also, the negative impact of the radicals can be neutralized through it. Quercetin is an antioxidant flavonoid known for its antiallergic anti-inflammatory, antiviral properties. It works as an anti-oxidant. However, during oxidation, a number of adverse substances are formed, including free radicals, which are extremely damaging. It prevents free radicals. These free radicals are said to destroy cells that are used to save your body against different types of infections created or caused in the body. They can even influence DNA functionality and increase the mutation of the cells, which most of the time results in damaged or dead cells. It has properties that are responsible for fighting factors that promote these free radicals and ensure a healthier body. It's great for energy and endurance. It's a natural anti-histamine. Actually, it stabilizes the mast cells actually produces histamine. If you are getting stung by something or you have seasonal allergies, quercetin can be wonderful to be taken. Quercetin is a flavoid that comes under the category of safe compounds, which can be a dietary supplement. Quercetin in the form of a glycoside is considered to be much useful and efficiently used. (TNF-α) which is necrosis factor-alpha, quercetin has the ability to hinder (LPS) Lipopolysaccharide and inhibit tumor TNF-α. Lipoxygenase (LOX) and cyclooxygenase (COX) are the two enzymes having the property of producing inflammation whose action can be inhibited by quercetin. As natural anti-inflammatory studies indicate, quercetin may be beneficial for conditions that may be associated with inflammation, such as certain cancers and different factors that contribute the heart disease either as single,

combined, encapsulated, or derived from, were evaluated employing only cell line models in vitro or both cell and animals models in vitro and in vivo. Maintaining cardiovascular health is essential for a healthy life. You can do it simply by incorporating quercetin into your daily life, and it could be in any form. Quercetin is a good source that protects our body cells from different types of health-related issues. (David et al., 2016) (Li et al., 2016) (Fernandez-Palanca et al., 2019).

I. Silibinin A

Milk thistle is a prickly plant that has distinctive purple flowers and white veins. It's an herbal supplement that detoxifies and protects viral liver functions. The active ingredient in milk thistle is a group of plants compounds collectively known as silymarin. Silibinin is obtained from silymarin. Milk thistle is able to help treat the liver condition. Silymarin is the main active ingredient in milk thistle. It is both an anti-inflammatory and antioxidant. It has the ability to treat liver disease and preventing from liver damage because of its beneficial antioxidant and its ability to reduce inflammation. It is particularly used for increasing the productivity of glutathione (a powerful antioxidant produced by the body) as well as increasing the levels of other antioxidants such as superoxide dismutase. Milk thistle seeds are the high source of the anti-oxidants flavonoid called silymarin. Silymarin is associated with decreasing the risk of cancer development by boosting the immune system fighting DNA damage, and revers in f cancerous tumor growth. It also has an antioxidant activity that has anti-cancer and anti-aging potential; antioxidants in milk thistle can defend skin from free radical damage. Milk thistle may protect your liver, and it is often promoted for liver protection. It is used as a complementary therapy by people who have liver damage due to conditions like alcoholic liver disease, non-alcoholic fatty liver disease, hepatitis, and even liver cancer. It's also used to protect the liver against toxins like amatoxin, which is produced by death cap mushroom and is deadly if ingested. The liver is actually the largest internal organ and is responsible for performing a number of essential detoxifying functions. Researchers think that milk thistle may be able to help treat liver conditions. An animal study from 2016 down that silymarin, an antioxidant extracted from milk thistles, has the potential to treat liver diseases and preventing in liver damage. This could be because of its beneficial antioxidants and its ability to reduce inflammation. Silymarin is associated with decreasing the risk for cancer development by boosting the immune system, fighting DNA damage, and reversing cancerous tumor growth. Silibinin can be used as a ligand in drug development because it has anticancer properties against liver cancer. Silibinin can be used in the case of hepatitis C. It can suppress the effect of hepatitis C infection in the early stages. Milk thistle has shown promise in its potential to benefit that your skin. An animal study from 2015 found that milk thistle applied topically had positive effects on inflammatory skin disorders. 2013 laboratory test indicated that milk thistle has an anti-oxidant activity that has anti-cancer and anti-aging potential. It's suggested that the antioxidants in milk thistle can cause defense skin from free radicals damage. (Bijak et al., 2017) (Christos et al.,2014) (Varghese et al., 2006).

J. Emodin

It's a chemical compound obtained from rhubarb, buckthorn, and Japanese knotweed. Emodin can be used to inhibit the growth of liver cancer cells. It has many other properties as well, like antioxidant, anti-alopecia, anti-diabetic, anti-cancer. LikeIndian medicine, traditional Chinese medicine is also used for a very long time. Much phytochemical information of plants can be found and obtained in china, and its information can be obtained by TCMSP server due to its low toxicity and other properties. Emodin is an anthraquinone derivative that is commonly found in a variety of different Chinese herbs, and it has the property of anti-proliferative in cancer. One of the major you find in it is next to allowing is Japanese knotweed is the bellowed Hu Shou Wu; Emodin is one of those wonder substances. One of the common benefits of Emodin is its ant estrogenic quality, so this is something that not many people know about Emodin. Emodin does a variety of different therapeutic benefits. It is important anti-inflammatory, it has important anti-diabetic, anti-estrogen, anti-obesity, or a weight-loss chemical biotic, or promoting oxidative metabolisms it's a profound neuroprotective herb that has anti-cancerous properties amongst many others; in fact, there are thousands of studies on beneficial therapeutic effects of Emodin (Xiaoxy et al.,2016). Emodin can be used as an anti-cancer for cancer because it induced apoptosis in HepG2 cells. And in the G1 phase, its significant accumulation of the cells can occur. The extrinsic and intrinsic can be suggested, activation of caspase-8 and caspase-9 can be done as when we treat cancer with Emodin it has been seen from the mitochondria the increasing of the release of cytochrome C into cytosol this is shown in western blot data. Emodin shows the accumulation of intracellular reactive oxygen species as a treatment result. Another function of Emodin is in HepG2 cells; it decreases the protein level of NF-kB/p65 and increases the protein p53. This shows that these two may play a role in apoptosis which is induced by Emodin. The computer-aided approach showed that Emodin could bind to Bcl-2, which comes under the domain of BH3 with the formation of one hydrogen bond in Bcl-2 with Ala146 residue. From the above function, we got to know that Bcl-2 can inhibit the heterodimerization of Bcl-2 with BAX because there is a strong interaction between Bcl-2 and Emodin, and hence it shows that it can also down-regulate the expression of Bcl-2Its anti-oestrogenic property, which is beneficial for a variety of reasons estrogen increases the production of cortisol which is a catabolic stress chemical oestrogen increases your cells affinity towards the water so it can lead to oedema or swelling or water retention oestrogen also generally opposes thyroid function. However, Emodin has many properties and can be used in a variety of diseases, but its anticancer mechanism for liver cancer is not clear (Hsu et al., 2012)(Dong et al.,2018).

K. Resveratrol

A natural phenol named resveratrol (two phenolic rings connected with styrene double bond product 3-4-5 trihydroxystilbene). It has two forms Cis and Trans, in which resveratrol of Transform has a wide-ranging effect. Resveratrol is basically an antioxidant which is the class of compounds that targets dysfunctional or abnormal cells in the body. It is found in the skin of grapes, blue barriers and has the highest natural concentration in Japanese nor weeds, which has been used in ancient medicine to treat inflammation for centuries. Research suggests that resveratrol selectively targets cancer cells by inhibiting cancer cell division migration and tumor growth-promoting cancer cell death. Several studies were done on the mouse in which they found that resveratrol has anti-inflammatory properties; polyphenol not only protects our body as an anti-oxidant but also activates autophagy in our body. The anti-oxidant and anti-cancer toxicity of resveratrol is very low. It has properties that can hold cancer cell growth and spread. It also activates the gene in our body called certulin 1, which switches off after about seventeen or eighteen years of age; it's a powerful anti-aging nutrient. It is also called the French paradox because the strength that resveratrol can give to the entire cardiovascular system is truly spectacular. There are thousands of studies around resveratrol, and it started all around the research of good cardiovascular health, so we know that a glass of red wine is good for health (Gambini et al., 2015). These different properties and studies show that resveratrol can be used as anti-carcinogen. Also, effect on hepatocellular carcinoma. Resveratrol can be easily available on regular bases because it has an effect on our body. Natural products are a good source for the treatment of any disease because only a few of them has minor side effects, but it has a potent effect against several diseases, in case of cancer it also has an anti-inflammatory and anti-cancer effect. Cancer development occurs when the mutation occurs in normal cells, and cells continue to grow, continuously making colonies and spread to other organs of the body like the liver, lungs, colon, and brain. Many good influencing effects of resveratrol have been seen at several stages of initiation, progression by affecting their pathways that control apoptosis, inflammation, and angiogenesis. We consider some compounds as potential anti-cancer agents which regulate oncogenic processes. It is so important for the brain it has an amazing power as an anti-oxidant. It can cross the blood-brain barrier, which means it increases the blood flow in the brain. It reduces the inflammation in the brain and gives an overall sense of a more youthful brain just by simple anti-oxidant effects. It supports good cardiovascular supports health. (Ko J et al., 2017)

L. Berberine

Liver cancer is the sixth most common cancer and second most common cause of cancer in the world. For cancer cells, proliferation glutamine metabolism is essential. Berberine belongs to alkaloids extracted from plants, including those known as the berberis family. It has been exploited for centuries, most notably in Chinese medicine, and is today becoming very popular in the western world as well. Berberine has several health benefits, which include promoting weight loss supporting blood sugar management, help reducing cholesterol level, reduce cancer risk, support liver health contain antibiotic properties may help control hypertension, can enhance female fertility and may assist with the management of the depression. Berberine is one of those compounds that are likely to fly your radar completely, even though it is actually one of the best natural compounds in the world. Anti-cancer properties can be revealed in recent studies done on the Berberine. There are several treatments available such as surgery, radiative therapy, chemotherapy, targeted drug therapy, alternative medicine, and immunotherapy. Some treatment options which can be used for early-stage treatments are ablation, liver transplantation, and liver resection. Berberine is one of the few nootropics active supplements known to activate adenosine monophosphate-activated protein kinase or AMPK for sure. This is especially relevant if you are diabetic, pre-diabetic, or over wait for all conditions that negatively affect cognition (Imenshahidi et al., nd). The early-stage treatment options are not suitable for advanced-stage liver cancer patient's treatment. For further use, absorption of glutamine is done, transporter which is Na+ dependence, transportation is done by SLC1A5. Different treatments and therapies are given to reduce or stop the growth and development of cancer cells and improve the lives of patients; in the present or recent time, researchers targets to determine the effect of bererine in cancer cell glutamine metabolism. Anti-cancer big time; in fact, there's a lot of studies going on using this Berberine on tumor and cancer. Berberine has several different properties like that Berberine has anti-cancer property also in this series the inhibitory effect of that can be seen with the help of two assays EdU and CCK-8, and the concentration of glutamine in Berberine is determined by UHPLC-MRM-MS and Enzyme-linked immune sorbent assay. Immuno fluorescent analysis, Western blot, and immunohistochemistry are some forms used to determine the proteins which are related to glutamine metabolism. Berberine has the ability that it can reduce the growth and development of liver cancer cells by reducing Glutamine uptake and SLC1A5 expression. The effect of Berberine in several cancer cells glutamine metabolism is not cleared. Researchers work on it (Zhang et al., 2019).

IV. Summary

The traditional drug development and discovery process is a very complex process that involves years of scientific research and trials, up to 14 years starting from lead identification to clinical trials. On top of the high costs incurred, a significant number of drugs fail to pass the clinical trials due to poor pharmacokinetic properties, insufficient specificity, and side effects. To solve this problem, Computer-aided drug design (CADD) came into existence which integrated computing power with the practice of medicine and brought about a revolution in the pharmaceutical industry. It provides us with a lot of benefits like low cost, time to market, speeding up the drug

discovery process, insight into the knowledge of interactions between drugs and receptors. Virtual Screening refers to the identification of leads or hits through computational methods. It utilizes a detailed database searching approach (commercial, public, or private 3-dimensional chemical structure databases) to find novel drugs for unexplored drug targets or alternatives to already existing drugs. It has been reported that hit rates, i.e., no. of compounds binding to the target divided by total no. of tested compounds, are 2 to 3 times more in virtual screening as compared to empirical screening.

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