A Review on: Role of Medicinal Plants in Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the fifth common tumor worldwide. In the United States, HCC is that the ninth leading cause of cancer deaths. HCC is the primary liver malignancy and could be a leading reason for cancer related death worldwide. Despite advances in prevention techniques, screening, and new technologies in both diagnosis and treatment, incidence and mortality still rise. HCC remains a global health challenge, with an estimated prevalence of >1 million cases by 2025. Multiple treatment options are available for HCC including liver transplantation (LT), radiofrequency ablation (RFA), trans arterial chemoembolization (TAF), radioembolization and systemic targeted agent like sorafenib. The treatment for HCC depends on the tumour stage, patient performance status. Among the past few years with significant advances in surgical treatments and locoregional therapies, the short-term survival of HCC has improved but the recurrent disease remains an enormous problem. Little progress has been made for this cancer, whose mortality is 100 % at 10 years. Progression from infection to cirrhosis takes average 20 years. The present study deals various medicinal plants that have a Pharmacological effect on HCC.

Keywords: Hepatocellular carcinoma, Liver transplantation, Radiofrequency ablation, Trans arterial chemoembolization, Radioembolization, Cirrhotic liver.

Introduction

Definition of cancer:

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably and spreads to other parts of the body.

Five main types of cancer:

- Carcinoma
- Sarcoma
- Melanoma
- Lymphoma
- Lukemia

Hepatocellular carcinoma (HCC):

Hepatocellular carcinoma (HCC) is the major form of primary liver cancer and is histologically and etiologically distinct from other forms of primary liver cancer. Nearly 70%–90% of cases with HCC have an established background of chronic liver disease and cirrhosis. It is a serious illness that can be dangerous. If it analysed early, hepatocellular carcinoma can be treated with surgery to remove the cancerous tumor or with a liver transplant.

Pathophysiology of HCC:

Hepatocellular carcinoma (HCC) mostly occurs in a cirrhotic liver, where repeated inflammation and fibrinogenesis predispose the liver to dysplasia and malignant transformation. Viral infections with hepatitis B virus

and hepatitis C virus lead to enhanced hepatocyte turnover as the liver attempts to change infected cells that have been immunologically attacked. There is some evidence to submit that HCC develops from hepatic stem cells that proliferate in response to chronic regeneration caused by viral injury. In small dysplastic nodules the cells appear to carry markers consistent with stem cells. HBV can also cause HCC in lack of cirrhosis. HBV integrates its deoxyribonucleic acid (DNA) within the host genome, leading to genomic instability and chromosomal rearrangements. HCV utilize ribonucleic acid (RNA) to store genetic information and therefore does not integrate within the host genome. HCV-related HCC is found exclusively in patients with cirrhosis. In the history, HCC in general presented at an advanced stage with right-upper-quadrant pain, weight loss, and signs of decompensated liver disease. However, routine screening of patients with known cirrhosis and α-fetoprotein (AFP) measurements has led to an increase in early discovery.

Signs and symptoms of HCC: Fever, Fatigue, Nausea and Vomiting, change in body weight, Lump, Skin infections, Abdominal pain, A persistent cough, Hoarseness, Change in bowel or bladder habits.

Diagnosis of HCC:

Blood Tests:

- Liver function test: A liver function test investigates the functioning of liver and to determine the health of your liver by measuring levels of proteins, liver enzymes, and bilirubin in your blood.
- Alpha-fetoprotein test (AFP): The presence of AFP in your blood can be sign of liver cancer. This protein is generally only produced in the liver and yolk sac of developing fetus. AFP production usually stops after birth.
- ALT (Alanine aminotransferase): An elevated ALT indicates liver disease or damage, including hepatitis.
- AST (Aspartate aminotransferase): As well as an elevated ALT, the AST checks for liver damage.
- Bilirubin: High bilirubin level suggests a problem with the liver.
- Albumin: As part of total protein level, albumin helps determine how well the liver is working.
- Ammonia: Ammonia level in the blood rise when the liver is not performing properly.
- Hepatitis A test: If hepatitis A is suspected, the doctor will test liver function as well as antibodies to detect the hepatitis A virus.
- Hepatitis B test: The doctor can test antibody levels to determine if you have been infected with the hepatitis B virus.
- Hepatitis C test: In addition to checking liver function, blood test can determine if you have been infected with the hepatitis C virus.
- Prothrombin Time (PT): A prothrombin time, or PT, is commonly done to check whether the patient is taking the correct dose of the blood thinner warfarin (Coumadin). It also checks blood clotting problems.
- Partial Thromboplastin Time (PTT): A PTT is done to examine for blood clotting problems.

Imaging Test:

- Ultrasound: An abdominal ultrasound can test for many liver conditions, including cancer, cirrhosis, or problem from gallstones.
- CT scan (Computed Tomography): A CT scan of the abdomen gives complete pictures of the liver and other abdominal organs.
- Liver biopsy: A liver biopsy is generally carried out after a blood test or ultrasound, that indicates a possible liver problem.

Current treatment:

- Surveillance: Surveillance used for lesions less than 1 centimeter found during screening. Follow-up every 3 months is common. Surveillance means watching a patient's condition closely. During active surveillance, certain tests are done on a regular schedule.
- Surgery: It is used to remove the part of the liver where cancer is found). A wedge of tissue, an entire lobe, a larger part of the liver, along with some of the healthy tissue around it is discard.
- Ablation therapy: In this therapy use of ethanol injections, heat, cooling to damage the cancer cells. It's usually performed using local anaesthesia. Ablation therapy includes:
- Radiofrequency ablation: Directly needles are inserted through the skin or through an incision in the abdomen to reach the tumor.
- Microwave therapy: The tumor is exposed to high temperature created by microwaves can damage cancer cells.
- Percutaneous ethanol injection: To kill cancer cells a small needle is used to inject ethanol (pure alcohol) directly into a tumor.
- Cryoablation: An instrument is used to freeze and damage cancer cells.
- Electroporation therapy: To destroy cancer cells electrical pulses are sent through an electrode placed in a tumor.
- Chemotherapy: It is a powerful form of drug therapy that damages cancer cells. The medications are given intravenously or through a vein. In most of the cases, you can receive chemotherapy as an outpatient treatment.

Advanced treatment:

- Liver transplant: In a liver transplant, the complete liver is removed and replaced with a healthy donated liver. A liver transplant may be done when in the disease in the liver only and a donated liver can be found.
- Embolization therapy: Embolization therapy is used for patients who unable to have surgery to remove the tumor or ablation therapy and whose tumor has not expand outside the liver. Embolization therapy is the use of substance to block or decrease the flow of blood through the hepatic artery to the tumor does not get the needed oxygen and nutrients; it won't continue to grow. Embolization therapy includes Tran's arterial embolization, Tran's arterial chemoembolization.
- Targeted therapy: It is a drug treatment that targets the cancer's specific proteins, genes or the tissue environment that contributes to cancer growth and survival. This treatment blocks the development of cancer cells and limits damage to healthy cells.
- Immunotherapy: Immunotherapy, also called biologic therapy, is designed to boost the natural defence to fight the cancer. It uses materials either by the body or in a laboratory to target, improve or restore immune system function. Immunotherapy is called an Immune checkpoint inhibitor.
- Radiation therapy: This therapy uses radiation in high-energy to damage cancer cells. It can be transferred by external beam radiation or by internal radiation. Certain methods of giving external radiation therapy can help keep radiation from damaging nearby healthy tissue. Radiation therapy includes Conformal radiation therapy, Stereotactic body radiation therapy, Proton beam radiation therapy.

Other chemotherapeutic agents:

- Atezolizumab is a type of immunotherapy drug that helps the body's immune system to fight against cancer. It is a monoclonal antibody immune checkpoint inhibitor that works by blocking a protein called programmed death-ligand 1 (PD-L1) that stops the immune system from working properly and attacking cancer cells.

- Bevacizumab is a recombinant monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A). Drug binds to soluble VEGF and inhibits the binding of VEGF molecules to its receptors on surface of endothelial cells. Binding of VEGF impairs endothelial cell proliferation and the formation of new blood vessels, which in turn reduces tumor growth and metastasis. It was the first available angiogenesis inhibitor in the United States.
- Cabozantinib-s-malate inhibits the specific receptor tyrosine kinases: c-MET (hepatocyte growth factor receptor protein) and Vascular endothelial growth factor (VEGF-2), c-RET, (GAS6 receptor) AXL, c-KIT, and FM's-like tyrosine kinase-3 (FLT3), MDR1.
- Pembrolizumab stimulates the body's immune system to fight against cancer cells. Pembrolizumab blocks proteins such as PD-1 on the surface of certain immune cells called T-cells. Blocking PD-1 triggers the T-cells to find and destroy cancer cells. Pembrolizumab by inhibiting lymphocytes' PD-1 receptors, blocking the ligands that would deactivate it and prevent an immune response.
- Regorafenib is a multikinase inhibitor which blocks tyrosine kinases that are very active in angiogenesis. Regorafenib has more activity against VEGF receptor. Regorafenib is a stronger inhibitor of c-KIT and partially blocks TIE2. This molecule is important in angiogenesis, potentially allowing regorafenib to be a stronger inhibitor of angiogenesis.

Prevention:

- Don't use tobacco products.
- Stay physically active, do some exercise.
- Maintain healthy lifestyle and healthy diet.
- Practice safe sex.
- Get vaccinated**.**

Ayurvedic remedies: Haldi (turmeric), Green tea, Milk thistle (Silybum marianum), Mangosteen (garcinia mangostana), Gioly, Ashwagandha (withania somnifera)

Cancer rehabilitation: There are some services and therapies which help a person maximize their functioning physically, emotionally, spiritually, socially, and financially.

- Physiatrist
- Rehabilitation nurse
- Physical therapists
- Lymphedema specialists
- Pulmonary therapists
- Speech-language therapists
- Nutritionists
- Counsellor's
- Recreational therapists
- Social workers

Aim and objectives

Aim: The aim of the present study was to estimate anticancer activity using various herbal plants of N-nitrosodiethylamine induced hepatocellular cancer.

Objectives:

- Cancer is a life threating disease in which there is an uncontrolled cell division or growth.

- Treatment with anti-cancer medicines and radiation increase Reactive oxygen species (ROS) and reduce antioxidants content, producing a state of severe oxidative stress and causing apoptosis, resulting in side effects, while persistent oxidative stress at sub lethal levels may result in resistance to apoptosis.
- Medicinal plants had been used by different cultures throughout the time for different medicinal purposes which are now promising sources for identification of lead molecules for cancer therapy.
- Reactive oxygen species are found to be alter the signal transduction pathways and the gene tumor suppressers such as p53 inactivation and thereby resulting in over expression of proto-oncogenes.
- Determination of the proliferation activities of each cell line in response to every plant extract treatment.
- Determination of % viability of every cell line in response to every plant extract treatment.
- Determination of any morphological changes of every cell line in each whenever performing viability testing assay in parallel.

Review literature

- **B. Kavitha et al (2018)** Plants have been a valuable source of natural products for maintaining human health. Indigofera mysorensis Rottl. exDC. Fabaceae, commonly known as Konda Vempali is a glutinous shrub in rural India used for its antidiabetic activity. The aim of the present work is to evaluate the invitro antimicrobial activity of aqueous and organic solvents extracts of leaves of I. mysorensis by agar well diffusion method using gram positive bacteria like Bacillus subtilis and gram-negative bacteria like Escherichia coli, Klebsiella pneumonia, Proteus vulgaris; fungal cultures are Candida albicans and Aspergillus Niger. The antibacterial and antifungal activity indicate their effective inhibition in comparison to that of the control drugs Ampicillin and Nystatin at 10mg/well. Physicochemical analysis was performed on the leaves of I. mysorensis.
- **Alagar RM et al., (2015)** studied of phytochemical and antioxidant activity of Cucumis melo var. agrestis fruit. Phyto chemical study reveals that carbohydrates, tannins, flavonoids, alkaloids, saponins, steroids & triterpenoids and glycosides were present in the extract. The antioxidant activity is performed by hydrogen peroxide in In vitro method on every extract and ethanolic extract showed important action towards free radicals.
- **Kripa S et al., (2015)** studied anti-dyslipidemic and anti-adipogenic potential of Cucumis melo ssp. agrestis var. agrestis (CMA). Oral administration of CMFE and both fractions (CMWF and CMHF) decreased the total cholesterol, triglycerides, low- density lipoprotein cholesterol, and very low- density lipoprotein-cholesterol levels in high fat diet-fed dyslipidemic hamsters. CMFE and CMHF also reduced oil-red-O accumulation in 3T3-L1 adipocytes. Depending on these results, we can conclude that CMA possesses anti-dyslipidaemia and anti-hyperglycaemic activity also with the anti- adipogenic activity.
- **Arirudran *et al.*, (2014)** Evaluated and examined the levels of minerals in serum and liver in DEN induced hepatocellular carcinoma in Wistar albino rats for possible chemo preventive effect. In hepatocellular carcinogenesis complications such as hepatic fibrosis and cirrhosis may lead to several abnormalities in mineral metabolism, hence attempt has been made to evaluate on the level of minerals. Concentration of calcium, magnesium, sodium, and potassium were assessed in the serum at the end of experimental period. Negative correlations were seen between liver function tests and serum mineral levels, except with albumin. Calcium, magnesium, potassium, and sodium concentrations in the serum has decreased after the induction of hepatic cancer. The calcium content has increased after DEN treatment. No changes occurred in liver sodium content. However, magnesium and potassium content were significantly reduced in the hepatic tissue. The results suggest that in DEN-induced hepatocellular carcinoma alteration of essential elements was noted. The low levels of albumin and related sites may be one of the major causes of the imbalance of mineral metabolism in hepatocellular carcinoma.
- **Srisesharam srigopalram *et al.*, (2012)** Evaluated the chemo preventive potential of *T. chebula* aqueous extract (TCE) by estimating the levels of lipid peroxidation and assaying activities of various marker

enzymes in diethyl nitrosamine (DEN) induced liver cancer. Oxygen free radicals generated by several processes *in vivo* are toxic and highly reactive. It is well known fact that oxidative stress arises when there is an imbalance between oxygen free radicals' formation and scavenging by antioxidants. Thus, the result has study confirmed the efficacy of TCE as an effective chemotherapeutic agent.

- **Arora R et al., (2011)** The study shows that methanolic extract of Cucumis melo var agrestic seeds has significant antioxidant activity which may be responsible for its anti-inflammatory and analgesic activity. Thus, extracted seed can be used to treat diseases caused by free radicals.
- **Naina Mohamed Pakkir Maideen *et al.*, (2011)** Evaluated the chemo preventive effect of methanol extract of *Phyllanthus polyphyllus* (MPP) against N-nitrosodiethylamine (DEN, 200mg/kg) induced experimental liver tumor in male Wistar rats. Administration of MPP (200 and 400mg/kg) completely suppressed liver tumor induced by DEN as exposed by decrease in DEN induced elevated levels of alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), alkaline phosphatase (ALP), gamma glutamate transpeptidase (GTP), lipid peroxidation (LPO) and alfa feto protein (AFP). The extract also produced an increase in total proteins and enzymatic antioxidants [superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx)] and non-enzymatic antioxidants [Reduced Glutathione (GSH), Vitamin C and E] levels when compared to liver tumor bearing animals. Our data suggest that MPP may extend its chemo preventive effect by modulating lipid peroxidation, liver enzymes and augmenting antioxidant defence system.
- **Ranjan basa *et al., (*2000)** Evaluated inhibition of diethyl nitrosamine induced rat liver chromosomal and the DNA-strand breaks by synergistic supplementation of vanadium and 1K,25-dihydroxyvitamin D3. This drug has inhibited growth and induced differentiation of a variety of cell types. Synergistic of both V and 1,25 (OH)2D3 DEN injection has found to offer significant protection against generation of single-strand breaks. The study results of elevation of the mitotic rate in the Liver. Therefore, it seems possible that the elevation of the mitotic rate during DEN treatment favoured production and increase in the number of cells with abnormal chromosomes, and the drug (vanadium and 1K,25-dihydroxyvitamin D3) shows an anti-hepatocarcinogenesis activity.

Medicinal plants

1. Annona Muricata (soursop also known as Graviola or Guanabana)

The family of Annona muricata is Annonaceae with genes and species named as Annona muricata. It also contains chemical constituents like 2-hexenoic acid methyl ester (23.9%), 2-hexenoic acid ethyl ester (8.6%), 2-octenoic acid methyl ester (5.4%), 2-butenoic acid methyl ester (2.4%), beta-caryophyllene (12.7%), 1,8-cineole (9.9%), linalool (7.8%), alpha-terpineol (2.8%), linalyl propionate (2.2%), and calarene (2.2%). This plant has few pharmacological activities like arthritic pain, neuralgia, arthritis, diarrhoea, dysentery, fever, malaria, parasites, rheumatism, skin rashes, and worms, it is also eaten to elevate a mother's milk after childbirth. From the seeds fresh ripened fruits pulp was separated, peels and dried in a hot-air oven at 50 °C. This material was then subjected to coarse powdering. This material was subjected to Soxhlet extraction using ethanol. The concentrated and dried A. muricata fruit (AMF)-extract was used for both in vitro and in vivo assays. The A. muricata fruit extract was further subjected to fractionation with chloroform, petroleum ether, and ethyl acetate. Each fraction was dried in a desiccator. The petroleum ether fraction, chloroform fraction (CHL-AMF) and ethyl acetate fraction were further considered for anticancer activity in HepG2 cells. For the experiment purpose, the animals were reported as Male Wistar rats of 12-week-old and (90-100) g weight were used for the DEN-induced HCC model. Then the animals were divided into 4 groups containing each of 6 rats and maintained at standard libitum. The experimental protocol as followed as Group 1 animals has received Normal control (NC), rats were fed with standard food and water. Group 2 animals have received disease control (DC), rats were fed with 0.01% of DEN in drinking water for 14-weeks. Group 3: AMF-Pre-treatment group, rats were co-administered AMF-extract (200 mg/kg, P.o.) from the first day (0th week) with DEN in drinking water for 14 weeks. Group 4: AMF-Post-treatment group, rats were induced HCC by administering DEN in drinking water for 8-weeks and then AMF-extract (200 mg/kg, P.o.) was co-administered with DEN in

drinking water till the 14th week. Hence, we concluded that the test sample has more effect when compared to the standard sample.

2. Aegle Marmelos (Bael, Bengal quince, Golden apple, Wood apple):

The family of Aegle Marmelos is Rutaceae with genes and species named as Aegle Marmelos. It also contains chemical constituents like coumarin, xanthotoxol, imperatorin, aegeline, and marmeline. This plant has few pharmacological activities like antidiabetic, anticancerous, antifertility, antimicrobial, immunogenic, and insecticidal activities. 500 g of coarsely dried powdered leaves were first extracted with petroleum ether followed by 70% ethanol by hot extraction process. After completion of extraction process the solvent was removed under reduced pressure and in vacuum desiccator the extract was stored till further use. For the experiment purpose, the animals were reported as male albino wistar rats weighing 180–200 g were used in the study. Then the animals were divided into 7 groups of 6 animals each and maintained at standard libitum. The experimental protocol as followed as group (i) has received normal control group (2 ml/kg distilled water). Group (ii) has received PCM group (400 mg/kg PCM). Group (iii) has received silymarin group (positive control, PCM 400 mg/kg + silymarin 200 mg/kg. Group (iv) has received A. Marmelos extract for 25 group (PCM 400 mg/kg + extract-25 mg/kg). Group (v) has received extract 50 group (PCM 400 mg/kg + extract-50 mg/kg). Group (vi) has received extract-100 group (PCM 400 mg/kg + extract-100 mg/kg). Group (vii) has received extract 25 + piperine group (PCM 400 mg/kg + extract-25 mg/kg + piperine 20 mg/kg). Hence, we concluded that the test sample has more effect when compared to the standard sample.

3. Catharanthus Pusillus (Murr.) (Tiny Periwinkle):

The family of Catharanthus Pusillus Apocynaceae with genes and species named as Catharanthus Pusillus. It also contains chemical constituents like linolenic acid ethyl ester, stearic acid, phytol and hexadecenoic acid. This plant has few pharmacological activities like antifungal, antibacterial, antiviral, anticancer, and antioxidant. The whole plant was shade dried and then powdered to obtain a coarse powder, which was then subjected to extraction in a Soxhlet apparatus using ethanol. The extract was tested for the identification of several phytochemical constituents as per standard procedures. In a rotary evaporator the ethanol extracts were concentrated. The concentrated ethanol extract was used for study. For the experiment purpose the animals were reported as Adult male wistar albino rats weighing about 180 – 240 g body weight were selected for this work. Then the animals were divided into six groups of 5 rats each and maintained at standard libitum. The experimental protocol as followed as Group 1 rats received normal saline (0.9%), by using an intragastric catheter tube (IGC)- Normal control. Group 2 liver injured rats received 2.5 ml/kg body weight of normal saline (0.9%) for 14 days, by using IGC, -CCl4 hepatic toxicity induced control. Group 3 Liver injured rats received C. Pusillus whole plant ethanol extract at the dose of 150 mg/kg body weight for 14 days, by using an IGC. Group 4 Liver injured rats received C. Pusillus whole plant e t h a n o l extract at the dose of 300 mg/kg body weight for 14 days, by using an IGC. Group 5 Liver injured rats received C. Pusillus whole plant e t h a n o l extract at the dose of 500 mg/kg body weight for 14 days, by using an IGC. Group 6 Liver injured rats received silymarin orally at the dose of 100 mg/kg body weight for 14 days, by using an IGC. Hence, we concluded that the standard has less effect when compared to the test sample.

4. Elephantopus Scaber (Tutup Bumi, Elephant’s Foot, Ironweed):

The family of Elephantopus Scaber is Asteraceae with genes and species named as Elephantopus Scaber. It also contains chemical constituents like 17,19-dihydroxyelephantopin, iso-17, 19-dihydrodeoxy elephantopin and 8-hydroxyl naringenin. This plant has few pharmacological activities like antidiabetic, anticancer, antitumor, anti-inflammatory. The plant has been broadly screened for anticancer activity. The plants were washed using running tap water followed by rinsing with distilled water. The plants were then cleaned, slashed, shade dried and powdered. 50g of dried powder was Soxhlet extracted with 400mL of solvents of raising polarity viz. petroleum ether, chloroform, methanol, and ethanol for 48h each. The extract was concentrated under reduced pressure in a rotary evaporator and was kept under refrigeration. The yield of methanolic extract was 10% (w/w). For the experiment

purpose, the animals were reported as Male Wistar rats weighing 150 ± 5.5 gm were used in this study. Then the animals were divided into five groups and maintained at standard libitum. The experimental protocol as followed as Group 1 has received Normal control. Group 2 has received NDEA control. Group 3 has received Silymarin treatment. Group 4 has received Elephantopus Scaber methanolic extract (100mg/kg). Group V - Elephantopus Scaber methanolic extract (200mg/kg). Group II-V rats received a single dose of 0.02% NDEA in water 5 days per week for 20 weeks. Hence, we concluded that the test sample has more effect when compared to the standard sample.

5. Leucas Aspera (Thumbai, Thumba):

The family of Leucas aspera is Lamiaceae with genes and species named as Leucas aspera. It also contains chemical constituents like beta-caryophyllene (34.2%), 1-octen-3-ol (14.8%), alpha-humulene (6.3%), alpha-pinene (5.8%), epi-alpha-bisabolol (4.6%), and limonene (4.5%). This plant has few pharmacological activities like analgesic, antipyretic, antirheumatic, anti-inflammatory and antibacterial. Coarse powder (250g) was subjected Soxhlet extraction using hydro alcoholic solvent (1:1 water: ethanol).8 The aqueous extract was prepared using the same marc by the process of maceration.9 Before oral administration to rats the extract was dissolved in normal saline. For the experiment purpose, the animals were reported as Healthy Wistar albino rats of either sex weighing between 150-180 g were taken for the study. Then the animals were divided into five groups of 6 rats each and maintained at standard libitum. The experimental protocol as followed as Group 1 has received Normal control received physiological saline solution, i.p. Group 2 has received Hepatocarcinogenic control (DEN 200 mg/kg i.p.) after two weeks. Group 3 has received Standard Synthetic Drug Cyclophosphamide (orally: 50 mg/kg body weight dissolved in sterile water), 2 weeks before DEN injection (200 mg/kg i.p.) and continued throughout the experimental period (i.e., 6 weeks). Group 4 has received Leucas aspera hydro-ethanolic extract treated group (200 mg/kg orally), 2 weeks before DEN injection (200 mg/kg i.p.) and continued throughout the experimental period (i.e., 6 weeks). Group 5 has received Leucas aspera Aqueous Extract treated group (200 mg/kg orally), 2 weeks before DEN injection (200 mg/kg i.p.) and continued throughout the experimental period (i.e., 6 weeks). Hence, we concluded that the test sample has more effect when compared to the standard sample.

6. Martynia Annua L… (Cat's claw, Tiger's claw, Iceplant):

The family of Martynia annua L... is Martyniaceae with genes and species named as Martynia annua (L..). It also contains chemical constituents like oleic acid, arachidic acid, linoleic acid, palmitic acid, gentistic acid, stearic acid, pelargonidin-3,5-diglucoside, cyanidin-3-galactoside, p-hydroxy benzoic acid, apigenin, apigenin-7-o-glucornide. This plant has few pharmacological activities like anthelmintic, analgesic, antipyretic, antibacterial, anti-convulsant, anti-fertility, antinociceptive, antioxidant, CNS depressant, and wound healing activity. After collection, the leaves were washed with water to remove dust and air-dried. After total dryness, using a blender the leaves were ground to a coarse powder, then passed through the sieve of 40 mesh and stored in a well closed container. This powdered plant material of Martynia annua L. leaves was extracted in a Soxhlet apparatus using petroleum ether (60-80EC) as solvents for defatting. The dried defatted powder material was extracted again with methanol. The solvent was then removed at 40EC under reduced pressure in a Rota evaporator. For the experiment purpose, the animals were divided into Wistar albino rats of either sex (100-150 g) were selected for the experimental study. Then the animals were divided into five groups of 6 rats each and maintained at standard libitum. The experimental protocol as followed as Group 1 has received animals were kept as control who received the vehicle for ten days at a dose of 1 mL kgG1 (P.o.). Group 2 has received animals were considered as positive and received dose for ten days every 72 hours. Group 3 received standard drug silymarin (100 mg kgG1) and CCl4 dispersed in sterile olive oil (1:1 v/v, 2 mL kgG1, i.p.) for 10 days. Group IV-V received methanolic extract at the dose 200 and 400 mg/kg/day, respectively (dispersed in 0.5% sodium carboxymethyl cellulose) and carbon tetrachloride dispersed in sterile olive oil (1:1 v/v, 2 mL kgG1) for 10 days. Hence, we concluded that the test sample has more effect when compared to the standard sample.

7. Plumbago Zeylanica Linn… (Wild white leadwort):

The family of Plumbago zeylanica Linn. is Plumbaginaceae with genes and species named as Plumbago zeylanica. It also contains chemical constituents like plumbagin, isoshinanolone, plumbagic acid, beta-sitosterol, 4-hydroxybenzaldehyde, trans-cinnamic acid, vanillic acid, 2,5-dimethyl-7-hydroxychromone, indole-3-carboxaldehyde. This plant has few pharmacological activities like antibacterial, antifungal, anti-inflammatory, antidiabetic, anticancer, antioxidant, hepatoprotective, cytotoxic, and wound healing. The rhizomes were powdered through nice clothes. For the experiment purpose, the animals were reported adult male albino Wistar rats (weight range: 110- 130 gm) were employed for this study. Then the animals were divided into three groups of 6 rats each and maintained at standard libitum. The experiment protocol as followed as Group 1 served as control and received the liquid paraffin only at the dose of 1ml/kg body weight along with standard feed and water ad libitum. Group 2 served as the hepatotoxic group and received carbon tetrachloride (CCl4) in liquid paraffin suspension intraperitoneal on alternate days for a week. Group 3 animals served as the treatment group, CCl4 was administered for two consecutive days and following 24 hours after the last injection, treatment was started by the oral administration of an aqueous suspension of test drug at a dose of 1g/kg body weight for 5 days. Hence, we concluded that the test sample has more effect when compared to the standard sample.

8. Rubia Cordifolia (Indian madder, Madder wort):

The family of Rubia cordifolia is Rubiaceae with genes and species named Rubia cordifolia. It contains chemical constituents which include anthraquinones, alkaloids, steroids, flavones, flavonoids, phenols, saponins, tannins, proteins, and glycosides. This plant has few pharmacological activities like wound healing, antibacterial, antioxidant, anticancer, anti-inflammatory, and analgesic, hepatoprotective, anti-platelet activating factor, anti-acne activity. 1 kg of RC roots were treated with petroleum ether of 2.5 L at room temperature in closed container and repeated till 7 days without allowing it to dry. By vacuum filtration the plants material was removed. The plant extract obtained from the above step was subjected to cold percolation using methanol (95%, v/v) as solvent and suitably concentrated by rotary pump vacuum evaporator and in a vacuum desiccator it was dried and stored at room temperature. It was dissolved in water and orally administered to rats. For the experiment purpose, the animals were reported as male albino wistar rats weighing between 120-150 gm for the study. Then the animals were divided into four groups and maintained at standard libitum. The experimental protocol as followed as Group 1 Control rats received normal diet and drinking water. Group 2 Rats were treated with DEN (0.02%) orally in drinking water. Group 3 Rats were given DEN (0.02%) in drinking water along with the methanol extract of RC (250, 500 and 750mg/kg body weight, respectively) orally. Group 4 Rats treated with RC alone (500mg/kg/body weight) orally. Hence, we concluded that the test sample has more effect when compared to the standard sample.

9. Symplocos Racemose (Lodh tree):

The family of Symplocos racemosa is Symplocaceae with genes and species named as Symplocos racemosa. It also contains chemical constituents like flavanol glucosides like symplocoside, symposide, leucopelargonidin-3-glucoside, ellagic acid, flavonol glycoside like rhamnetin-3-digalactose, triterpenoids like 19 alpha-hydroxyarjunolic acid-3, 28-O-bis-beta-glucopyranosides, 19 alpha-hydroxyasiatic acid-3, 28-O-bis-beta-glucopyranosides, botulin, oleanolic acid, beta-sitosterol, and alpha-amyrin. This plant has few pharmacological activities like diarrhoea, dysentery, liver diseases, uterine disease leprosy, anticancer, hepatoprotective, antioxidant, anti-androgenic effect, anti-inflammatory, wound healing activity and anti-diabetic's effect. The bark was coarsely powdered and defatted with petroleum ether (60-80º C). The marc was subjected to maceration for 7 days in ethanol (95%) with daily occasional shaking. This ethanol extract of S. racemosa (EESR) was evaporated to dryness under reduced pressure (% yield = 6% w/w). For the experiment purpose, the animals were reported as Wistar rats (150-200 g) and albino

mice (20-25 g) for the study. Then the animals were divided into five groups of 5 rats each and maintained at standard libitum. The experimental protocol as followed as Group 1 (Normal Control) was served as control and received 2% acacia solution. Groups 2 (CCl4 Control) to V were injected daily with a mixture of CCl4 and olive oil (1: 1) at a dose of 0.2 ml/kg, i.p. for 10 days. Group 3 (Silymarin) served as the standard group and were administered silymarin (100 mg/kg, P.o.). Groups 4 (EESR200) and 5 (EESR400) were treated with 200 and 400 mg/kg, P.o. EESR, respectively, for 14 days. Hence, we concluded that the test sample has more effect when compared to the standard sample.

10. Tinospora Cordifolia (Guduchi):

The family of Tinospora Cordifolia is Menispermaceae with genes and species named as Tinospora cordifolia. It also contains chemical constituents like alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides. This plant has few pharmacological activities like anti-diabetic, anti-spasmodic, anti-malarial, anti-inflammatory, anti-arthritic, antioxidant, anti-allergic, anti-stress, anti-leprotic, hepatoprotective, immunomodulatory, anti-neoplastic activities. The dried leaves which are shaded were pulverized and subjected for extraction using pet ether, ethanol (LR grade, Merck, India) and aqueous separately using Soxhlet apparatus. Using rotary flash evaporator, (Buchi Flawil, Switzerland) the extracts were concentrated. Th e suspension of extracts were prepared using 5% gum acacia and used for the study. For the experiment purpose, the animals were reported as Wistar strain albino rats (150-200 g) for the study. Then the animals were divided twelve groups of 6 rats each and maintained at standard libitum. The experiment protocol as followed as group 1 received three doses of 5% gum acacia mucilage (1ml/kg b.w.) at 12 h intervals (0 h, 12 h and 24 h). The rats of CCl4 group 2 received three doses of vehicle at 12 h intervals and a single dose of CCl4 (1.25ml/kg b.w.) diluted in liquid paraffin (1:1) 30 minutes after administration of 1st dose of vehicle. Group 3 served as reference control, received silymarin (25mg/kg b.w.) once daily for 3 days. Group 4 to 12 received, T. cordifolia extract (200 mg/kg b.w.) once a day for 3 days. Group 3 to 12 received CCl4 (3gm/kg b.w.) as single dose on day 3, thirty minutes after the administration of extracts and silymarin respectively. Hence, we concluded that the test sample has more effect when compared to the standard sample.

Conclusion

Cancer is one of the life-threatening diseases which creates major problem in both developing and developed countries. Liver cancer is the second leading cause of cancer-related death, and an alarming number of new liver cancer cases are expected every year. Primary liver cancer remains a primary health problem with great geographic variability. Men are at an advanced trouble of developing liver cancer compared to women. Liver cancer occurs generally in men with liver disease caused by hepatitis B or C virus, alcohol consumption, or hemochromatosis. Initial manifestations are typically abdominal pain, palpable abdominal mass, and constitutional symptoms similarly anorexia and weight loss. Most of the present cancer chemotherapeutics and surgery, chemotherapy, radiotherapy, hormonal therapy is associated with harsh and undesirable side effects, including toxicity and chemoresistance, driving the need for safer and more effective treatment alternative. Liver transplantation and hepatic resection are the curative options in early stage of disease. There have been important advances in local ablative and trans arterial therapies. In the starting-stage HCC, RFA is equivalent to surgical resection in well-selected patients. Drug eluting beads have enhanced the efficacy and safety of conventional TACE. Cancer patients experience many varied physical, psychological, and socio-economic problems according to their cancer type and treatment state and have a need for rehabilitation services associated with their problems. We expect that this study will provide preliminary data for developing appropriate cancer rehabilitation programs and making policies. Hepatic diseases are a main trouble to public health, indicating problems to the hepatic tissue or to the liver functions, which can be caused by different factors, similar as viruses or bacteria, autoimmune diseases, or by the external action of different chemicals (medicines or toxic compounds). Currently, modern medicine offers alternatives for the treatment of these pathologies, but despite the advances, few effective drugs that offer protection and regeneration of hepatic cells exist.

Though liver disease is among the most important disease affecting mankind, no remedy is available at present in the modern system of medicine which include corticosteroids and immunosuppressive agents. Additionally, their use is associated with the risk of relapses and danger of side effects. An actual curative therapeutic agent has not yet been established and thus management of liver disease is still a challenge to the modern scientific community. Consequently, increasing attention is being given to plants recommended for the treatment of hepatic disorders in traditional system of medicine. A few medicinal preparations have been supported especially in Ayurvedic system of Indian medicine, for the treatment of liver diseases.

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