LITERATURE REVIEW
The fruits of *Piper cubeba* (Piperaceae) commonly known as Kabab-chini, Java Pepper, Tailed Cubebs, Tailed Pepper is used to treat various diseases. The fruits of this plant possess medicinal properties and are used in treatment of Hepatitis. *P. cubeba* is used in mixtures given as a tonic during confinement. Other, *P. cubeba* is used as an aphrodisiac. Due to its stimulant, antiseptic and diuretic actions on the mucous membrane of the genitourinary organs, it has been used for a long time to treat gonorrhea. It is also prescribed to relieve fever, asthma, sunstroke, vomiting, rheumatism, malaria, leucorrhoea and peripheral neuritis. In addition, this plant has been used in Taiwan to treat gonorrhea and diabetes, and it is also used to stimulate the appetite and to aid digestion. However, prolonged use may cause diarrhoea. In Indonesia, *P. Cubeba* is the one of the content in native medicines to treat venereal disease, dysentery and other intestinal disorders. In China, the fruits are known to be used as a stomachic and carminative. They are used as a remedy for vomiting, abdominal disorders, indigestion and amoebic dysentery. The fruit is also ingested to treat coughs, bronchitis, sinusitis, sore throats and genitourinary infections.

The dried *P. cubeba* fruits contain essential oil consisting of monoterpenes: sabinene, β-elemene, α-thujene, carene, 1,4-cineol and 1,8-cineol; sesquiterpenes: b-caryophyllene, copaene, α- and β-cubebene, d-cadinene, cubebol and germacene; and some lignans including the dibenzylbutyrolactone lignan i.e. (-) cubebin. (Wiart. et al., 2006). The active chemicals from dried fruits of *P. cubeba* like 5- methylenedioxyphenyl lignans, (-)-clusin, (-)-dihydroclusin, (-)-yatein, (-)-hinokinin, and (-)-dihydrocubebin, were reported as potent and selective inhibitors against cytochrome CYP3A4. (Usia et al., 2005).

Other chemical constituents are allo-aromadendrene, α-murolene, α-phellandrene, α-pinene, α-terpinene, α-terpineol, asarone, β-bisabolene, β-pinene, bicyclosesquiphellandrene, calamene, cesarone, cubebic acid, cubebinolide, cubenol, epicubenol, g-humulene, g-terpinene, gum, ledol, limonene, linalol, myrcene, nerolidol, ocimene, resinoids, sabinol, and safrole. (Dr. Duke’s). In the partial synthesis from (-)-cubebin yielded (-)-O-Acetyl cubebin, (-)-O-benzyl cubebin, (-)-O- (N,N-dimethylaminoethyl) - cubebin, (-)- hinokinin, (-)-6,6’-dinitrohinokinin, and (-)-6,6’-diaminohinokinin. (De Souza. et al., 2005). Derivatives of cubebin: (-)-O-acetyl-, (-)-O-
methyl-, (-)-O-dimethylethylamine cubebin were synthesized, in an attempt to improve the analgesic and anti-inflammatory activities of cubebin. (Souza G.H.B. et al., 2004). The fruits of this plant was reported for free radicals scavenging ability, antioxidant activity, anti-inflammatory and antinociceptive activities.

Aboul-Enein et al., (2011): Identified the antioxidant activity of 16 isolated compounds from Piper cubeba (CNCs) through the extent of their capacities to scavenge free radicals, hydroxyl radical (HO•), superoxide anion radical (•O2−) and 2,2-diphenyl-1-picrylhydrazyl radical (DPPH•), in different systems.

Adriana P. F. Junqueira et al., (2007): Observed the male and female Swiss mice and Wistar rats and the comet assay and micronucleus test investigation of the mutagenic potential of a crude extract of P. cubeba seeds. The extract induced a statistically significant increase in both the mean number of micronucleated polychromatic erythrocytes and the level of DNA damage in the rodent cell types analyzed. The P. cubeba seed extract was found genotoxic in vivo when administered orally to mice and rats.

Gayatri N. et al (2011): Observed the Piperine is an alkaloid found naturally in plants belonging to the pyridine group of Piperaceae family, such as Piper nigrum and Piper cubeba. It is widely used in various herbal cough syrups and anti inflammatory, anti malarial, anti leukemia treatment. Ethanol extract of Piper cubeba shows high antioxidant activity.

Eun-Mi Choi et al., (2003): Studied the anti-inflammatory activities of Piper cubeba (fruit), Physalis angulata (flower) and Rosa hybrid (flower) was determined by carrageenan-induced paw edema, arachidonic acid-induced ear edema and formaldehyde-induced arthritis in mice. The anti-allergic and analgesic activities of these plants was studied by using 2,4-dinitrofluorobenzene (DNFB)-induced contact hypersensitivity reaction (type IV) and hot plate test in mice, respectively.

Tepy U. et al., (2005): Studied the mechanism of inhibition of CYP3A4 by lignans and the possibility of their mechanism-based inhibition. Using [N-methyl-14C] erythromycin as a substrate, all lignans appear to be showed mixed-type of inhibition with apparent Ki of 1.96–4.07 μM. Furthermore, all lignans (1–5) inhibited CYP3A4 in a time-
concentration-, and NADPH-dependent manners and thus appear to be the mechanism-based inhibitors of CYP3A4.

_Silva M. L. A. et al., (2007)_: Investigated the crude ethanol extract from _Piper cubeba_ seeds, (-)-cubebin and its semi-synthetic derivatives was evaluated against oral pathogens. The presence of the carbonyl group at C-9 plus the introduction of polar groups in the aromatic rings increases the antimicrobial activity of dibenzylbutyrolactone compounds.

_Mohamed S. TS et al., (2008)_: Studied the hepatoprotective effect of extracts of _Annona squamosa_ in isoniazid + rifampicin induced hepatotoxic model. Significantly decrease in total bilirubin, increase in the level of total protein and decrease in ALP, AST, ALT and γ-GT. The extracts of _Annona squamosa_ was not able to revert completely hepatic injury induced by isoniazid + rifampicin, but it decreases the effect of these drugs in liver. The effect of extracts compared with standard drug silymarin.

_Ravi V. et al., (2010)_: Studied the hepatoprotective activity of methanolic extract of flowers of _Bombax ceiba_ L. (MEBC) against hepatotoxicity produced by administering a combination of two anti-tubercular drugs Isoniazid and Rifampicin for 10 and 21 days by intraperitoneal route in rats.

_Bihari P. B. et al., (2009)_: Investigated the extract of aerial part of _Jatropha gossypifolia_ was screened for its hepatoprotective activity in carbon tetrachloride induced liver damage in Wister albino rats.

_Gayatri G et al., (2011)_: Studied the hepatoprotective activity of Ethanolic extracts of _Stachytarpheta indica_ (whole plant) on Wistar rats. Liver damage was induced by intraperitonal administration of carbon tetrachloride (1ml/kg,b.w,p.o) for 7 days, by using silymarin as a standard drug.

_Sambo N. et al., (2009)_: Studied the effect of _Psidium guajava_ extract on erythromycin-induced liver damage in albino rats. The aqueous extract of _psidium guajava_ leaf shows the hepatoprotective property at lower dose and a hepatotoxic property at higher dose.

_Zakaria Z. A. et al., (2011)_: Investigated the hepatoprotective effect of MARDI-produced virgin coconut oils, prepared by dried- or fermented-processed methods, using the paracetamol-induced liver damage in rats, Liver injury induced by paracetamol.

Ali S.A. et al., (2009): Studied the aqueous and methanolic extracts of *Capparis decidua* stems screened for hepatoprotective activity against CCl4-induced hepatotoxicity in rats. The hepatotoxicity produced by administration of CCl4 in paraffin oil (1:9 v/v), toxicity inhibited by simultaneous oral administration of aqueous and methanolic extracts of *C. decidua* stems with evidences of decreased level of serum aspartate amino transferase, alanine amino transferase, alkaline phosphatase and bilirubin.

Karthikeyan M. et al., (2011): Investigated the hepatoprotective activity of ethanolic extract of *Spermacoce hispida*Linn (SHE) against carbon tetra chloride (CCl4) induced hepatotoxicity in rats. Liver functions assessed by the determination of the SGOT, SGPT, ALP and bilirubin.

Gond NY et al., (2008): Studied the Petroleum ether (60-80°) extract of *Ficus carica* tested for antihepatotoxic activity on rats treated with 50 mg/kg of rifampicin orally. The biochemical parameters assessed serum levels of glutamic oxaloacetate transaminase, glutamic pyruvic transaminase, bilirubin and histological changes in liver. Liver weights and pentobarbitione sleeping time as a functional parameter monitored. The significant reversal of biochemical, histological and functional changes induced by rifampicin treatment in rats by petroleum ether extract treatment, indicating promising hepatoprotective activity.

Lahon K. et al., (2011): Investigated the Leaves of Sacred/Holy Basil, i.e. Green Tulsi (*Ocimum sanctum*), belonging to family Lamiaceae used for hepatoprotective effect. The *Ocimum sanctum* alcoholic leaf extract shows significant hepatoprotective activity and synergism with silymarin.

Morita T. et al., (2003): Evaluated the hepatoprotective activities of spices, 21 different spices were fed to rats with liver damage caused by lipopolysaccharide (LPS) plus D-galactosamine (D-GalN). Nutmeg showed the most potent hepatoprotective activity. Myristicin major essential oil of nutmeg shows the potent hepatoprotective activity.
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Manokaran S et al., (2008): Investigated the hepatoprotective activity of hydroalcoholic extract of Aerva lanata against paracetamol induced liver damage in rats. The hydroalcoholic extract of Aerva lanata (600mg/kg) administered orally to the animals with hepatotoxicity induced by paracetamol (3gm/kg). Silymarin (25mg/kg) given as reference standard. The plant extract effective in protecting the liver against the injury induced by paracetamol in rats.

Shyam Kumar B. et al., (2010): Studied the diethyl ether extract of Coccinia indica leave for hepatoprotective activity against carbon tetrachloride induced liver toxicity in rats. The hepatoprotective activity of Coccinia indica leave extract at dose 400 mg/kg body weight comparable with standard treatment 125 mg/kg body weight of silymarin.

Gnanasekaran D. et al., (2012): Evaluated the hepatoprotective activity of the whole plant Indigofera tinctoria on the Chang cell line (normal human liver cells). The ethanolic extract tested for its inhibitory effect on chang cell Line. The percentage viability of the cell line carried out. The cytotoxicity of Indigofera tinctoria on normal human liver cell evaluated by the SRB assay [Sulphorhodamine B asssay] and MTT assay [(3-(4,5 dimethylthiazole –2 yl)-2,5 diphenyl tetrazolium bromide) assay]. The principle involved is the cleavage of tetrazolium salt MTT into a blue coloured derivative by living cells which contains mitochondrial enzyme succinate dehydrogenase.

Jamshidzadeh A. et al., (2006): Studied the effects of different concentrations of the hydroalcoholic extract of dried powdered leaves of Cichorium intybus L., on CCl4-induced hepatotoxicity in vivo in rats. The Cichorium intybus extract could protect the liver from CCl4-induced damages with doses of 50 and 100 mg/kg, but concentrations higher than 200 mg/kg less effective.

Mohamed B. A. et al., (2008): Investigate the ameliorative activity of aqueous extract of the flesh of dates (Phoenix dactylifera L.) and ascorbic acid on thioacetamide-induced hepatotoxicity in rats. Thioacetamide-induced liver damage in rats can be ameliorated by administration of extract of date flesh and ascorbic acid.

Aghel N. et al., (2011): Studied the protective action of Ficus carica leaf ethanolic extract (obtained by maceration) evaluated in animal model of hepatotoxicity induced by carbon tetrachloride (CCI4). Levels of marker enzymes such as alanine aminotransferase (ALT)
and aspartate aminotransferase (AST) increased significantly in CCl4 treated mice. Pre-treatment with the extract resulted in less pronounced destruction of the liver architecture with no fibrosis and moderate inflammation observed. The treatment with Ficus carica leaf extract in dose of 200 mg/kg enhanced protection against CCl4 induced hepatic damage.

Patial K et al., (2011): Investigated the protective action of C. trigonus fruit extracts evaluated in study in animal model of hepatotoxicity, toxicity induced by carbon tetrachloride.

Wu-Yi Sun et al., (2008): Investigated the effects of P. lactiflora and A. membranaceus extract on immunological liver injury in mice induced by Bacillus Calmette-Guérin and lipopolysaccharide (BCG/LPS) and to explore a possible mechanism. After administration of P. lactiflora and A. membranaceus, the extract significantly reduced the degree of liver damage in BCG/LPS-induced liver injury, as well as the elevation of serum transaminase activities and level of nitric oxide in live injury mice. The P. lactiflora and A. membranaceus have a protective effect on BCG/LPS-induced liver injury mice, associated with the antioxidant properties, ability to reduce nitric oxide production and suppression of Kupffer cell activity and pro-inflammatory mediator and cytokines production.

Patere S. N. et al., (2009): Investigated the effects of oral treatment with polyherbal formulation Normeta on hepatic damage induced by alcohol 10–30% (blood alcohol maintained at levels between 150 and 350 mg/dl), thermally oxidized oil (polyunsaturated fatty acids) (15% of diet) and carbonyl iron (1.5–2% of diet) for 30 days in rats. In vitro studies with 1, 1-Diphenyl, 2-Picrylhydrazyl (DPPH), Nitric oxide and Ferric chloride (Fe+3 ions) show Normeta possesses antioxidant and metal chelating activity. The effect of Normeta on physico-metabolic parameters comparable with silymarin. This indicates Normeta shows favourable effect in bringing down the severity of hepatotoxicity.

Sengupta P. et al., (2010): Studied Olanzapine-induced hepatopathy models in rats used for screening putative hepatoprotective agents and in this model silymarin has failed to provide any hepatoprotection. Hence Olanzapine-induced hepatopathy models in rats is one of the best model for screening.
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**Mankani K. L. et al., (2005):** Evaluated the hepatoprotective activity of methanol extract of Pterocarpus marsupium stem bark against carbon tetrachloride (CCl4)-induced hepatotoxicity in male Wistar rats. Methanol extract of the stem bark of P. marsupium shows significant hepatoprotective activity.

**Pornpen Pramyothin et al., (2007):** Studied the protective effect and possible mechanism of aqueous extract from *Phyllanthus amarus* Schum. et. Thonn. (PA) on ethanol-induced rat hepatic injury. In the *in vitro* study, PA (1–4 mg/ml) increased % MTT reduction assay and decreased the release of transaminases (AST and ALT) in rat primary cultured hepatocytes being treated with ethanol. Histopathological observations show the beneficial roles of PA and SL against ethanol-induced liver injury in rats. Possible mechanism shows antioxidant activity.

**Pattanayak S. et al., (2011):** Investigated the hepatoprotective activity of crude flavonoids extract of *Cajanus scarabaeoides* (L) in paracetamol intoxicated albino rats. The crude flavonoids extract of *Cajanus scarabaeoides* (L) shows hepatoprotective activity.

**Sangameswaran B. et al., (2008):** Evaluated the hepatoprotective effect of *Andrographis lineata* (Acanthaceae) extracts in carbon tetrachloride-induced liver injury in rats. The pharmacological evidences support the folklore claim that it is used as a hepatoprotective agent.