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Role of natural phenolics in hepatoprotection: A mechanistic review and analysis of regulatory network of associated genes

Role of natural phenolics in hepatoprotection: A mechanistic review and analysis of regulatory network of associated genes

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Introduction

The liver is labelled as the biggest glandular organ that controls diverse physiological and chemical processes in human body. In other words, it plays a central role in metabolic control and detoxification involving metabolism of lipids, carbohydrates, alcohol and a wide range of drugs as well as toxins (Aseervatham et al., 2018). The liver also participates in innate immune function (Gao et al., 2008).Interestingly, the liver has the unique ability to regenerate and completely recoup from most acute, non-iterative situation (Mosedale and Watkins, 2017;Oliva-Vilarnau et al., 2018). However, multiple conditions, e.g., hepatitis, chronic alcohol consumption, frequent use of antibiotics associated medications and also even non-alcoholic fatty liver disease can affect the regenerative efficacy of the hepatocytes, which become totally dysfunctional(Forbes and Newsome, 2016), generally witnessed by the visible hepatic scaring, apoptosis and entering into most severe cirrhosis. The liver, when witnesses such atrocities, ultimately loses its vitality and thus imbalances the normal metabolic phenomenon leading to many other fatal conditions (Branco et al., 2016;DeFronzo et al., 2016). Despite considerable amounts of research have been carried out aiming at curing various hepatic ailments across the world, limitation still does exist in finding more effective hepatoprotective drugs than the currently available medications. Moreover, fewer medications promise in restoration effect.

The Mediterranean-style diet which covers the immense geographical area adjoining the Mediterranean Sea focuses the use of root legumes, vegetable, fruits, nuts and seeds predominantly (Tuck and Hayball, 2002). Presently there is an arising concern rather interest

in exploring the positive effects of plant-based diet for mitigating various chronic diseases including several hepatic ailments like hepatic cirrhosis, hepatic ulcerative syndrome and fibrosis. It is noteworthy that Mediterranean diet has been allied with many health benefits, is characterized by a high intake of fruits, vegetables and nuts containing several bioactive natural products of plants. One of such dietary component common in plant-based diets are natural phenolics, which are particularly plentiful not only in fruits, whole grains, vegetables and legumes but equally in coffee, tea, cocoa and also in red wine.

Phenolics are a bulky and heterogeneous group of phytochemicals containing phenol rings and are divided into several group viz; phenolic acids, flavonoids and lignin. Amongst fruits like pears, grapes, apples and range of berries naturally contain good amounts of polyphenols (250–400mg in 100 g). The most frequent phenolic acids are ferulic acid and caffeic acid that comprises of major phenolic compound in coffee and cereals, respectively. Most studied stilbene is resveratrol in red wine and grape products (Veberic et al., 2008). Other main dietary sources of natural phenolics comprises of chocolate, green tea and whole grains. Polyphenol contains abundant antioxidants in the diet and this act as natural scavengers for toxic elements and thus their intake has been directly connected with a reduced frequency of several hepatic ailments particularly hepatocellular carcinoma in humans (Turati et al., 2014). Phenolics also exhibit anti-inflammatory effects and influences hepatotoxicity through altered mechanisms discussed in details in the subsequent paragraph.

Thus, herbal approach, an alternative to the conventional protocol with a touch of a therapeutic essence, remains a valid option. These strategies, in most cases, not only target the disease but also are with minimum side effects. Majority of the available synthetic drugs for liver diseases are found to be strong pro-oxidant scavengers, but their long-term uses may cause inflammation (Rani et al., 2016;González-Ponce et al., 2018) and cancer. A noteworthy instance is the use of tiopronin, which increases the risk of liver injury ten folds with its long-term treatment (Tang et al., 2014;Wan and Jiang, 2018). Another well-illustrated detrimental combination is ribavirin and interferon-α (IFN-α), a common medication in liver-related diseases, which is seen to affect hepatitis C patients. Taking into consideration of such complications and high cost of available medicines, researchers are inclined to utilise natural products-based alternative medications for liver diseases, which will have better efficacy, cost-effectiveness and lower or no toxicity (Zhang et al., 2013;Seeff et al., 2015).

It is evident from the reports of the WHO (WHO 2016) that non-communicable diseases were the causes of 68% of all global death in 2012 (Figure 1), rising from 60% in2000. Hepatic complications have turned out to be multifactorial diseases that affected almost around 600 million population in 2014 (Figure 2) and it is likely to amplify about 33% over the next two decades(Finkelstein et al., 2012;Dhilleswara Rao et al., 2017).

PLEASE INSERT FIGURE 1 HERE

Figure 1: Statistical representation of mortality (in percentage) from various diseases in human(Finkelstein et al., 2012).

Hepatic ailment results in anomalous hypertrophy, expressed phenotypically with surplus adiposity, body fatness and brawny genetic correlation with its constituent to basal metabolic index and associated health hazard of obesity have also been reported(Locke et al., 2015;Stender et al., 2017).

PLEASE INSERT FIGURE 2 HERE

Figure 2: Occurrence and Prevalence of various liver diseases worldwide

Various hepatic problems are encountered with a number of synthetic as well as plant-based drugs. Nexavar is a chemotherapeutic drug generally prescribed for complex renal carcinoma (Ravaud et al., 2016;Decker et al., 2017). It is additionally used to treat liver carcinoma. Known adverse effects of Nexavar include usually dry skin, itching, skin rash, nausea, vomiting, diarrhoea, patchy hair loss, loss of appetite, stomach pain, dry mouth, hoarseness and tiredness(Schmidinger and Bellmunt, 2010). Sorafenib is the first multi-kinase inhibitor (TKI) approved for the treatment of advanced hepatocellular cancer (HCC) metastatic renal cell cancer (RCC), and well-differentiated radioiodine-resistant thyroid cancer (DTC)(Monsuez et al., 2010). It demonstrates targeted activity on several families of receptor and non-receptor tyrosine kinases that is involved in angiogenesis, tumour growth and metastatic progression of cancer(Adnane et al., 2006). Sorafenib is a well-known antihepatotoxic drug available in market but the product of its metabolism has been seen to be toxic, which affects other parts of the body with long-term exposure resulting in renal and pancreatic failure (Randrup Hansen et al., 2017;Balderramo et al., 2018).

A few efficient varieties of herbal preparation like Liv-52, silymarin(Kolasani et al., 2017) and Stronger neomycin phages (SNMC) are in attendance against hepatic complications. All the candidates come up with notable complications. Silymarin is not found effective against chronic liver disease as it fails to modulate the metabolic condition of the liver along with cellular recovery. An effective Japanese preparation like SNMC(Ghiliyal and Bhatt, 2017) also fails to improve the clinical status with liver cirrhosis inspite of its prominent anti-inflammatory and cytoprotective efficacy. It is successfully used against hepatocellular carcinoma(Luo et al., 2015). Liv-52 is used quite effectively against hepatic damages (Stickel and Hellerbrand, 2015). However, it also fails to demonstrate clinical efficacy in alcoholic liver damages. Various research involving techniques with increasing efficacy of the phytochemicals like nanotechnology, proteomics, transcriptomics are evident and efforts are going on with herbal preparation are someway successful too (Patil et al., 2018). Taking the clue, from these interesting results, further attempts should be initiated to overcome all the odds of existing drugs, and an initiative may proceed with plant-based natural products. The plants are an enormous repository of bioactive secondary metabolites viz; alkaloids, flavonoids, phenol, etc. This review presents an account of studies on phenolics with its emphasis on it mechanism of towards hepatotoxicity. Emphasis have been given to understand various pathways through which phenolics exihibit their effecicacy. Furthermore a gene networking model has been constructed to have a clear concise idea of natural phenolics contributing in mitigating various hepatic ailments.

Methods

With the aim to evaluate the actual sceneries of phenolic compounds for the treatment of various hepatic diseases, a search on the metabolic disease Library and PubMed has been performed matching the keywords “hepatic disease inhibitors treatment,” “target therapy,” and “Hepatic carcinoma,” limited to the English written literature, but with no restriction of time. It was examined and the titles of 202 relevant papers were retrieved.

While performing through the search of abstracts and full-text research papers, all the unrelated and less important ones was discarded. Selection of the most recent and well-illustrated cited full-text articles were considered regarding similar types of research work from the same institute at different point of time. We have tried not counting the research papers, whose abstract or full-text is not obtainable. The references for significant and relevant papers have been further sought for other pertinent articles. After such an illustrative survey, around 160

latest bioactivity reports of phenolic compounds mitigating hepatic diseases were brought into lights and also around 38 clinical trials have been retrieved gratifying the indispensable criteria for analysis.

Gene networking model and connectivity model was developed by analyzing all the available reports on the hepatoprotective activity of the natural phenolics using the online software Cirrcon and Cytoscape version 3.6.1.

Natural molecules as potent antihepatotoxic agent

Plant secondary metabolites are well-known for their efficacy in the treatment as well as prevention of various fatal diseases. Plant phenolics, e.g., coumarins, flavonoids, lignans, stilbenoids, and tannins, have been studied extensively to provide scientific rationale behind their potential usage against various human ailments. Phenolics are the target group for this review article and subsequent discussions will revolve around exploring chemical nature, and modes of action of these compounds(Smith, 2017;Stander et al., 2017).

Phenolics constitute a major portion of all plant secondary metabolites discovered to date, and there are about 8000 of such compounds in both conjugated and free-form and distributed in all parts of the plant. Phenolics are generally biosynthesized from acetyl CoA, shikimate and amino acids(Cseke et al., 2016;Saltveit, 2017). Plant phenolics include simple phenols, phenolic acids, coumarins, lignans, flavonoids, diaryl-alkanoids, stilbenoids, proanthocyanins, and anthocyanins some alkaloids, and tannins.

Natural product has been an integral part of medicine since ancient times where, around 400 different species of plant and animal origins were then listed. According to the WHO, till now, plant based therapy are into action, where minerals, plants are common and easily available. Such accounts for around 88% of the population, where they depend on the natural product from their primary health care regime. Though the term ‘drug discovery’ sounds contemporary, yet the story of drug discovery dates back many centuries, where it has origin in its nature. Thus, present day uses of plants for ‘lead molecule’ discovery confirms its activity as active natural molecule or its structural analogue that can prove to be an ideal drug candidate.

Natural products drug discovery is on air in recent years with a comeback in the main stream of drug discovery protocols. Such comeback is welcomed by academics and also pharma companies mainly due to inherent chemical diversities in natural products, and ease in

identification and separation techniques. Noteworthy among natural products include alkaloid, carbohydrate, glycosides, terpenoids. Phenolics are most studied due to their antioxidant activities. The phenolic moiety is responsible for various pharmacological effects (Sarker and Nahar, 2007).

Phenolic acids are mainly represented as derivatives of benzoic acid and cinnamic acid. The methyl ester of the phenol ring imparts a pharmacophore, which is responsible for interacting various protein targets present in cell membrane. Gallic, ellagic, vallic, procatecutic, procoumaric and caffeic acids are important representative of hydroxyl benzoic acid hydroxyl cinnamic acid, which are the product of condensation reaction of phenols under sunlight(Ahmad et al., 2016;De Beer et al., 2017). Flavonoids on the other hand, biosynthesised from cinnamic acids, have two benzene rings (ring A and ring B), and apyrrole ring (ring C). Plant flavonoids are generally classified into flavan, flavanone, flavanol, flavone and flavonols (Sarker and Nahar, 2007).Often there are prenylations, glycosidations and conjugation with other ring systems or natural skeletons as well as dimerisations and oligomerisations diversify flavonoid structures and provide new pharmacophores. Quercetin, hesperidin, diosmetic, myrectin and kaempferol are just a few notable examples imparting biological properties(Hussain, 2016;Brodowska, 2017).

PLEASE INSERT FIGURE 3 HERE

Figure 3: Structures of various groups of Phenolic compounds (Hussain, 2016;Mandal et al., 2017;Xi et al., 2018)

PLEASE INSERT FIGURE 4 HERE

Figure 4: Flowchart showing various descendants of the Phenolic groups.

Anthocyanidins and anthocyanins are normally plant pigments. Anthocyanidins are grouped into 3-hydroxyanthocyanidins, 3-deoxyanthocyanidins, and *O*-methylated anthocyanidins. On the other hand, anthocyanins are in the forms of anthocyanidin glycosides and acylated anthocyanins (Sarker and Nahar, 2007). The most common types of anthocyanidins are cyanidin, delphinidin, pelargonidin, peonidin, petunidin, and malvidin(Wallace and Giusti, 2015;Chorfa et al., 2016;Makila et al., 2016;Stein-Chisholm et

al., 2017). The site of glycosylation in anthocyanidins is usually at C-3(Kay et al., 2017;Rodriguez-Amaya, 2018;Zhang et al., 2018).Acylated anthocyanins are presented with *p*-coumaric acid, ferulic acid and caffeic acid with attached sugar molecules, in addition to simple acetyl group (Sigurdson et al., 2017;Zhao et al., 2017).

PLEASE INSERT FIGURE 5 and 6 HERE

Figures 5 and 6: Structures of some bioactive phenolics acting as hepatoprotective compounds

Phenols are important as prospective drug leads

Phenolic compounds are known for their diverse chemical structures, common antioxidant and specific anti-inflammatory actions. They offer protection against oxidative damages by donating hydrogen or electron to free radicals and thus in this process they aid in stabilizing cell membrane networks and inhibit the formation and expression of inflammatory cytokines like tumour necrosis factor alpha (TNF-α), Transforming Growth Factor beta (TGF-β) and varieties of interleukins (IL-6, IL-2, IL-8)(Parhiz et al., 2015;Taofiq et al., 2015;Zhang and Tsao, 2016;Zhen et al., 2016).

PLEASE INSERT FIGURE 7 HERE

Figure 7: Metabolism of phenols in the living system. *The metabolism of the dietary components rich in phenols is easily absorbed by various part of the animal body where the small intestine process and deviates the potent part to hepatic cells and remains are hydrolysed in colon and excreted via faeces. Simultaneously, a part of it is methylated in kidney through liver and the last remains are excreted through urination. The red arrows mark is used to show the various route of metabolism of phenols.*

To exert any pharmacological or biological actions, phenolic compounds initially areabsorbed in the gastrointestinal tract (GIT) and thus make it bioavailable to circulating system. In the case of inadequate or no absorption through the GIT, they undergo biotransformation in the colon with the help of resident microbiota culture (Filannino et al., 2015;Heleno et al., 2015;Gómez-Juaristi et al., 2018). Phenolic compounds offer health benefits including treating cancer, oxidative damage and inflammation. Literature supports their effectiveness against chronic pathogenic conditions like neurodegenerative and cardiovascular diseases (Heleno et al., 2015;Rangel-Huerta et al., 2015;Domínguez-Avila et al., 2017).

Detailed mechanism of hepatoprotection

When the liver is exposed to alcohol, drugs, and pollutants, its progression towards damage initiates hepato steatosis, fibrosis and cirrhosis. This exposure results in the death of hepatocytes and as a consequence, level of various liver enzymes and metabolites are altered indicating the anomaly (Sheriff et al., 2017;Balderramo et al., 2018;Hu et al., 2018). Hepatocytes may be injured in various circumstances like toxic environment, alcohol, virus, fatty acid metabolism or chronic antibiotics exposure. Transaminases and glutathione are reported to be prime candidates' marker in the line up metabolism of bile when hepatocytes are damaged. The clinical condition of the hepatic environment can further be measured with level of alkaline phosphatase (a key hepatic enzyme) in the serum(Culver, 2016).

Under these surroundings, scarring tissues tries to replace the damages, and thus compromising with the vital liver functions like drug detoxification, secretion of the protein, albumin production etc(Anand and Garg, 2015;Baker, 2015). Metabolism, detoxification, and clearing of many drugs are blocked with the impaired liver(Bhattacharyya et al., 2014;Sheriff et al., 2017). Although there are several cited important bioactivity of phenolic compounds, the current discussion will primarily encircle around exploring detailed mechanisms of actions, and further contributions of phenolics against various liver damages.

Oxidative stress and hepatotoxicity: The liver being a keen partner and prime neighbour of the GIT is usually exposed to toxicity arising from the broad range of drugs, xenobiotics and also the stress mediated by reactive radicals formed during uncontrollable oxidation processes. Being a frequent target of such complex substances, and possessing unique metabolism system, it hampers itself in the process of breaking them into simpler ones (Cederbaum, 2017b). For instances, the large amount of bile acid produced during oxidation of ethanol produces hepatocellular apoptosis by exciting Fas, an apoptotic element, expressing it from in the plasma membrane triggering apoptosis resulting in cholestatic disease(Cederbaum, 2017). The liver also efficiently expresses main cytochrome P_{450} isoforms in response to various xenobiotics. CYP2E1 is one such that generates reactive oxygen family, activates toxicologically central intermediates, and may be the critical alleyway by which these toxic chemical groups cause oxidative stress. Further, kupffer cell, a specialized cell in liver is activated in this process of metabolism. Both Kupffer cell activation and infiltration of neutrophil release reactive oxygen

species (ROS), a range of inflammatory chemokines increasing the fold of hepatotoxicity (Wang, 2015;Ahadpour et al., 2016).

In vivo and *in vitro* studies have demonstrated the promising preventive and therapeutic effects of plant phenolics in a range of liver diseases. Translational studies are extremely vital and indispensable for the application of phenolics in human with liver diseases. Although literature in the PubMed database about clinical trials of phenolics in liver diseases are limited, encouraging beneficial effects of these phenols have been demonstrated, particularly in Non-Alcoholic Fatty Liver Disease (NAFLD). When working with the high fed diet, the AKT signal molecule responsible for fat metabolism is mutated in the model systems, placebo-inhibited trial of a purified form of anthocyanin in NAFLD patients, treating with the fixed amount of purified anthocyanin for three months significantly improved insulin resistance, in liver injury(Zhang et al., 2015a), and clinical evolution in such patients (Bischoff et al., 2018). In another double-blind clinical trial, dihydromyricetin, the main active ingredient of *Ampelopsis grossedentata*, improved glucose and lipid metabolism and showed anti-inflammatory effects in NAFLD(Chen et al., 2015b;Hou et al., 2015). When working with the hepatotoxic model system, the mice cohort which was treated with thioamino acetic acid showed significant recovery in its MAPK and AMPK level, the two important pathways, which imparts cAMP and are a source of energy to the hepatocytes. This recovery waswitnessed when a most studied flavonoid, curcumin was administered at a dose of 118µg/kg b.wt.

Alcohol and hepatotoxicity: Alcohol hinders the functional aspects of various tissue components and hepatocytes in particular. Alcohol diffuses crossing the membrane barrier and distributes throughout the cell and tissue system, interacting with the major proteins and cellular component present in it (Li et al., 2016). Development of toxic molecules like reactive oxygen species (ROS) is another pessimistic upshot of alcohol. In addition to ROS, it also produces acetaldehyde and nitric oxides, an extremely reactive and toxic by-product that chip into tissue damage (Madrigal-Santillán et al., 2015;Marshall, 2016). Nitric oxide (NO) is recognized to manage mitochondrial respiration and biogenesis amongst organelle. Under conditions of alcohol-mediated hepatic complications, mitochondrial respiration hindered, and inturn hypoxia occurs. Simultaneously, nuclear factor-kappa β (NF-κβ), a transcription factor activation takes place, where it binds to iNOS promoter, an important NO and aggravate the expression of iNOS(Iwakiri and Kim, 2015;Starkel et al., 2016). This entire environment

together amplifies the expression of inducible nitric oxide synthase (iNOS).iNOS joins hands in inducing hepatic fibrosis and expression of inflammatory cytokines(Tacke and Zimmermann, 2014;Cassini-Vieira et al., 2015). iNOS increases two other factors in this process. Hypoxia-inducible factor-1 and its gene expression aids in various connected hepatic anomalies viz; inhibition of mitochondrial respiration, impairment of mitochondrial fatty acid β-oxidation and mitochondrial DNA damage (Chang et al., 2015;Suraweera et al., 2015).

PLEASE INSERT FIGURE 8 HERE

Figure 8: Detailed Mechanism of generation of hepatotoxicity

When the elicitors like alcohol, CCl_4 enters the cell membrane they instigate various metabolic reactions activating the CYP systems viz; activating the endogenous glutathione enzyme, hydrogen peroxide. Formation of the reactive oxygen species are responsible for the lipid peroxidation reaction.A conjugation reaction parallel takes place resulting in the deterioration in the ATP levels and elevation in the caspases levels. These clinical manifestation leads to the building up of hepatotoxicity and induces apoptosis. The nucleus also takes part in such build up by upregulating various transcription factors associated with inflammation. The adhesion molecules present in the cell membrane further creates hepatic fibrotic response by coupling with various reactive oxygen species. The activated Kupffer cells on the other hand, further activate the prostaglandin by COX-2 and thus increases the cytokines level in the blood. These reactions are catalyzed by arachidonic acid. All such atrocities give rise to associated diseases with inflammation and further fibrogenesis. Hepatic necrosis is another condition imparted by the activated neutrophil which are though inactive during a normal state, increases its number when the cytokine level increases in the blood. The fatal condition, hepatic cirrhosis is also encountered from hepatotoxicity, which is the additive effect of the prolonged inflammation and interaction with the ROS generation.

Phenolics possess immense potentials in regulating the inflammatory cytokines, which are expressed in clinical conditions such as alcoholic liver diseases (Wan and Jiang, 2018;Xu et al., 2018). Puerarin, a known isoflavone, can excite the AMP-activated protein kinase (AMPK) phosphorylation in H4IIE cell lines suppressing the (m TOR) target proteins and 4E-binding protein (Zhao et al., 2016). This strategy aids in ameliorating the alcohol-based hepatotoxicity. Puerarin can also alleviate the hepatic necrosis due to its role in the AMPK pathway activation, scavenging activity and lipid peroxidation inhibition (Wang et al., 2018a).

PLEASE INSERT FIGURE 9 HERE

Figure 9: Alcohol mediated Hepatotoxicity. *Hepatotoxicity caused by increased production of ROS; due to alcohol damages antioxidant defences and mitochondrial function as well as structure. It leads to liver inflammation, fibrosis and steatosis. Cellular responses, which are sturdily involved in Kupffer cell may also activated due to action of ROS which contribute to an increase inflammatory*

responses resulting liver injury. Furthermore, activated Kupffer cells release ROS and cytokines that are crucial forHSC activation and to induce the pro-fibrogenic pathway.

Hepatotoxicity and non-alcoholic liver disease: Majority of the metabolic disorders and their physiology related to hepatotoxicity has been studied over the years. Where sharp and clear possible elements responsible for chemical-induced toxicity, enzymes and protein-induced complications are considered, yet a fair amount of diseases related to metabolism yet leftovers unidentified. Such prognostic parameters include blood pressure, abdominal obesity or may be hyperglycaemia. They are collectively termed as the non-alcoholic fatty liver diseases (NAFLD)(Chalasani et al., 2018).This clinical situation is one of the most familiar and dormant forms of liver diseases, which accounts for the preliminary stage, but when left untreated this results in the inflammation and subsequently can even lead to serious fibrosis and even hepatocellular carcinoma (HCC) with high rates of mortality(Chen et al., 2015a)

Until now, the main drugs for the treatment of NAFLD in the clinics are lipid regulating agents such as statins, which are not only toxic but also aggravate the deposition of lipids in the liver, leading to serious liver injury(Arguello et al., 2015). Phenolics such as baicalin, epicatechin and apigenin (Figure 5) have been reported to protect the liver from NAFLD, which are associated with their effects on insulin resistance and signaling way related to anti-inflammation as well as antioxidant action (Sen and Chakraborty, 2017;Wan and Jiang, 2018).

Phenolic compounds can significantly regulate these NAFLD conditions. Apigenin, a flavone, is a well-studied phenolic compound that can check the lipid accumulation and oxidative stress induced by high-fat diet. It can abridge the inflammatory mediators but can simultaneously amplify various endogenous antioxidative enzymes actions like superoxide dismutase, glutathione peroxidase in the liver (Feng et al., 2017;Vergani et al., 2017).Dihydromyricetin, another important phenolics exhibit its therapeutic effect by the improvement of glucose and lipid metabolism in patients with NAFLD, by blocking the phosphatidyl inositol 3-kinase, NF-κβ signaling pathway(Chen et al., 2015b).

Hepatotoxicity and inflammation: Liver inflammation is a state of the reaction in which the liver tissues send a constant stimulus whether acute or chronic, in response to extrinsic and intrinsic factors hampering the liver status. Acute inflammation is a localized affair, where the liver tries to regain its previous configuration. It is the first line of defence, but when the liver

cannot check these associated level of lymphocytes, vascular proliferation and tissue destruction become chronic and ultimately leads fibrotic condition (Pawlak et al., 2015;Leyva-López et al., 2016).

During such chronic conditions, specialized cells such as macrophages recruit more of the inflammatory mediators including interleukins, tumour necrosis factor (TNF)-α(Seki and Schwabe, 2015;Williams et al., 2016). This amplification altogether results in such a more complex state that it leads to many degenerative diseases including most severe cirrhosis and hepatic carcinoma(Czaja, 2014). For this reason, slowing down the inflammation process becomes essential. Initially, non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed but the associated side effects include mild gastritis, renal failure and at times allergy due to hypersensitivity(Pawlak et al., 2015)

Recent information on hepatic inflammation demonstrated the role of phenolics in protecting such inflammation. Phenolic compounds like hesperidin can act against inflammation by downregulating liver enzyme biomarkers such as aspartate amino transferase (AST) and alanine aminotransferase (ALT) primarily. It can also hold back oxidative stress and activation of T cells, which is a prime instigator of inflammation (Li et al., 2014). Hesperidin, a common *Citrus* flavonoid, further aids in the management of various proinflammatory recruiters viz; NF-κβ and α smooth muscle actin (α-SMA). Another well-known flavone, silymarin, is also a subclass of the family of phenolic compounds that works in patients with chronic hepatic carcinoma (González-Gallego et al., 2014).

PLEASE INSERT FIGURE 10 HERE

Figure 10: Protective effect of phenols in various metabolic pathways in liver diseases. *The upward arrow indicating upregulation and down arrow indicating downregulation of the enzymes.*

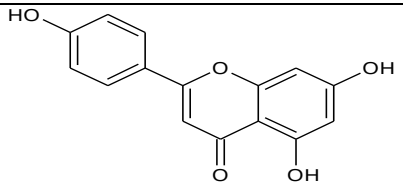
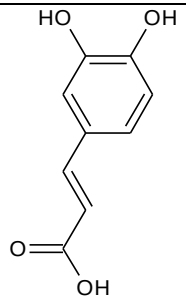
Regulation of gene expression by phenolics

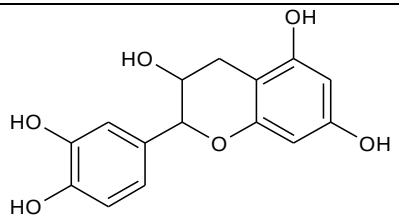
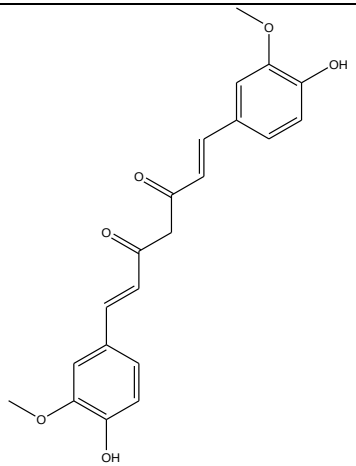
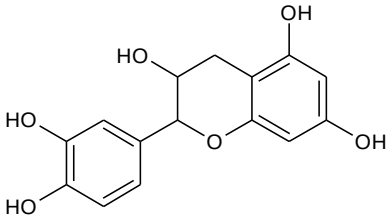
The chemical nature, physical properties and dose ratio of a particular drug along within dividual's gene expression profile, antioxidant status and the capacity for regeneration are also crucial for cell injury. Several mechanisms are involved in the initiation of liver cell damage and aggravate ongoing injury processes(Guan et al., 2014;Ju and Tacke, 2016). Dysfunction of

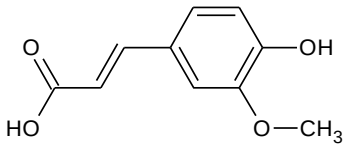
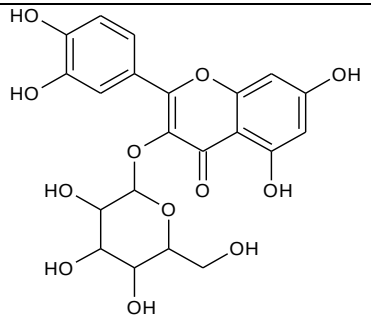
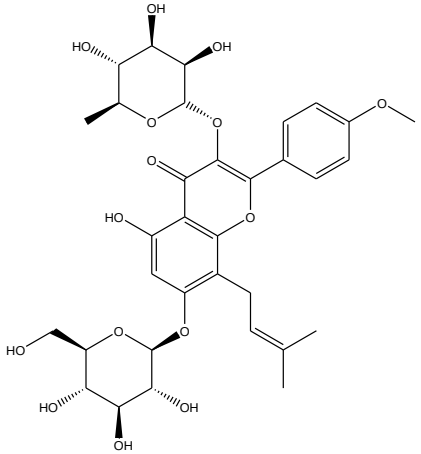
these vital cell organelles results in impairment of dynamic equilibrium in homeostatic condition, thus resulting in intracellular oxidative stress with excessive formation of reactive oxygen species(Cannistrà et al., 2016;Ramachandran et al., 2018). Major causes of the hepatotoxic reactions by drugs are elevated ROS generation, oxidative stress and suppressed immune responses. Hepatotoxicity remains a major cause of drug withdrawal from the market. Recent examples in the USA and Europe are ximelagatran, nefazodone, nimesulide, ebrotidine, trovafloxacin, troglitazone, bromfenac, and so forth.

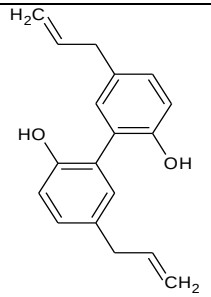
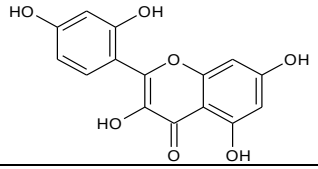
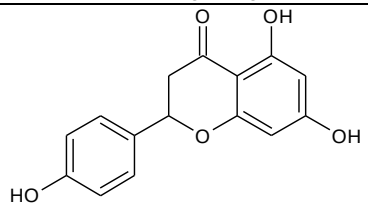
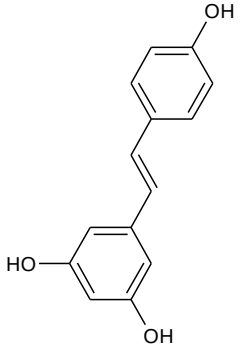
Gene-metabolic networks are an advanced mode to construct a network with genes and metabolites specifically deregulated in different liver disease phenotypes. It compactly gives an overview of genes of interest, representative gene subsets that were involved in regulated signaling pathways, including tumor necrosis factor(TNF), P53, NF-κB, chemokine, peroxisome proliferator activated receptor (PPAR) and Toll-like receptor (TLR) signaling pathways associated with the physiology of various hepatic disease. Detailed information for the clinical status and associated genes in the hepatotoxicity are summarized in gene networking model Figure 12. Gene regulation of a few bioactive phytocompounds is discussed below in Table 1

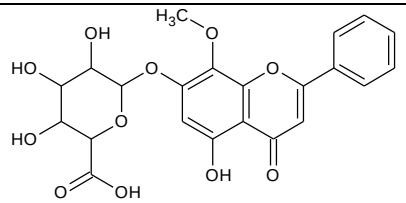
Table1: List of a few potent natural phenolics and their mode of action imparting hepatoprotective activity

Sl No.	Compound Name	Sub Category	Type of Liver disease	Structure	Mode of Action	Reference
1	Apigenin	Flavone	Hepatic ischemia/reperfusion		Up regulating BCL-2 levels	(Tsaroucha et al., 2016)
2.	Caffeic acid	Phenolic acids	Diabetic Liver injury		lipid peroxidation and antioxidant enzymes	(Yilmaz et al., 2004)

3.	Catechin	Flavonols	Hepatic tissue injury		antifibrotic and antioxidative	(Kobayashi et al., 2010)
4.	Curcumin	Curcuminoids	Non-alcoholic steatohepatitis		Immunomodulatory	(Nafisi et al., 2009)
5.	Epicatechin	Flavonoids	Diabetic Liver injury		Lipid peroxidation and antioxidant enzymes Effects of (–)-epicatechin, a flavonoid on lipid peroxidation and antioxidants streptozotocin-induced diabetic	(Terao et al., 1994)

					liver, kidney and heart.	
6.	Ferulic acid	Phenolic acids	Carbon tetrachloride (CCl_4)-induced acute liver injury		antioxidant, anticancer, and anti-inflammatory	(Kim et al., 2011)
7.	Hyperoside	Flavonol	Liver injury		Enhancement of APAP clearance	(Choi et al., 2011)
8.	Icariin	Prenylated flavonol glycoside (Flavonoid)	Hepatic fibrosis		Anti-angiogenic and anti-autophagic	(Algandaby et al., 2017)

9.	Magnolol	Neo-lignan	Immune-related liver fibrosis		Anti-inflammatory and antioxidant effects	(Ogata et al., 1997;Lin et al., 2001)
10.	Morin	Flavonoid	Hepatic fibrosis		Suppressing canonical NF-κBsignaling.	(Sivaramakrishnan and Devaraj, 2009;MadanKumar et al., 2014)
11.	Naringenin	Flavanone	Hepatic inflammation		activation of an Nrf2-mediated pathway	(Totta et al., 2004;Yen et al., 2009)
12.	Resveratrol	Stilbenoid	Alcoholic fatty liver		Inhibition of sirtuin 1 (SIRT1) and AMP-activated kinase (AMPK)	(Frémont, 2000;Baur and Sinclair, 2006)

13.	Wogonoside	Flavonoid	Hepatic fibrosis		Antifibrotic	(Yang et al., 2013)

PLEASE INSERT FIGURE 11 HERE

Figure 11: Gene networking showing hepatotoxicity mediated gene expression and subsequent mode of action of various natural product**s.** This network was generated by a software Cytoscape version 3.6.1.

TABLE 2: Table showing various hepatic diseases and various genes and metabolites associated with it

COMPOUND	HEPATIC DISEASES	CLINICAL CONDITION	TARGET	FAMILY	REGULATION	INVOLVED IN EXPRESSION	REFERENCES
Amentoflavone	microsomal lipid peroxidation	Fatty liver disease	COX-2	inflammatory mediators	inhibition	AP-1(downregulation)	(Arannilewa et al., 2006;Yadav et al., 2016)
Baicalein	hepatic apoptosis, inflammatory liver injury	acute liver apoptosis	IκBα, ERK and JNK	inflammatory mediators	downregulation	NF-κβ (down regulate)	(Meng et al., 2018) (Liu et al., 2015)
Caffeic acid	inflammatory liver injury	acute liver failure	c-FLIPL, XIAP and cIAP2 proteins	apoptotic protein	activation	NF-κβ (down regulate)	(Shi et al., 2018)
	inflammatory liver injury	acute liver failure	c-FLIPL, XIAP and cIAP2 proteins	apoptotic protein	activation	TNF-α (down regulate)	(Wang et al., 2018b)
	hepatic lipid peroxidation	Alcoholic fatty liver disease (AFLD)	glutathione reductase(GSH)	antioxidant enzymes	increase	microsomal ethanol-oxidizing system(increase)	(Chu et al., 2015)
Clofibrate	hepatic excessive proliferation	HCV-mediated hepatocellular carcinoma (HCC)	Cyp4a10 and Cyp4a14	mRNA expression of factors	increase	Acox1, Ech1, and Ehhadh (increased) Lipe and Pnpla2 (increased)	(Moody and Reddy, 1978;Bogdanska et al., 2018)
Galangin	microsomal lipid peroxidation	Fatty liver disease	COX-2 and iNOS	inflammatory mediators	inhibition	NF-κB (downregulation)	(Ren et al., 2016)
Gardenin D	microsomal lipid peroxidation	Fatty liver disease	COX-2	inflammatory mediators	inhibition	AP-1(downregulation	(Toppo et al., 2017)
Glabridin	chronic inflammatory liver disease	acute or chronic hepatitis and	PPARγ (peroxisome proliferator-				(Li et al., 2018) (Thakur and Raj, 2017)

			activated receptor gamma)				
	chronic inflammatory liver disease	hepatic steatosis	CCAAT enhancer binding protein alpha (CEBPα)	inflammatory mediators	downregulation	Phosphoenol pyruvate carboxykinase and glucose 6-phosphatase (downregulate)	(Namazi et al., 2017)
			cytochrome c,				(Lin et al., 2017)
Hispidulin	hepatic lipid peroxidation	Alcoholic fatty liver disease (AFLD)	glutathione reductase(GSH)	antioxidant enzymes	increase	microsomal ethanol-oxidizing system(increase)	(Wu and Xu, 2016;Han et al., 2018)
Icariin	hepatic excessive proliferation	HCV-mediated hepatocellular carcinoma (HCC)	PPARα	mRNA expression of factors	inhibition	Cpt1a, Acat1, Acad1 and Hmgcs2 (increased)	(Lee et al., 1995;Lu et al., 2014)
Kaempferol	fatty liver diseases	liver fibrosis	iNOS, COX-2 and CRP protein level	inflammatory mediators	downregulation	NF-κβ (down regulate)	(García-Mediavilla et al., 2007) (Kashyap et al., 2017)
	fatty liver diseases	liver fibrosis	(IRS-1) (IKKα) and (IKKβ).	inflammatory mediators	downregulation	kappa-β (NF-κB), (TNF-α) and (IL-6) (down regulate)	(Dong et al., 2017)
Kolaviron	liver inflammation	primary biliary cirrhosis	COX-2 and iNOS	inflammatory mediators	inhibition	NF-κB and AP-1 (downregulation)	(Adaramoye and Lawal, 2015;Awogbindin et al., 2015)
Liquiritigenin	hepatic failure	liver cirrhosis and hepatocellular carcinoma	PGC-1α, ND1, and Bcl-x	metastasis mediators	upregulation	apoptosis (downregulate)	(Yu et al., 2015;Li et al., 2018)
		liver cirrhosis and hepatocellular carcinoma	AMPK		activation	FXR (promote expression)	(Teng et al., 2016)

Luteolin	liver injury	fatty liver development	SREBP-1c	transcriptional factors	activation	cholesterol biosynthesis (activation)	(Seydi et al., 2018)
		hepatic steatosis	AMPK	energy sensor	activation	ATP-producing catabolic pathways	(Lee et al., 2006;Cummins et al., 2018)
						, such as FA oxidation(activation)	(Kwon and Choi, 2018)
		liver cirrhosis and hepatocellular carcinoma	iNOS	inflammatory mediators	downregulation	NF-ƙβ (down regulate)	(Jung et al., 2017)
	hepatic diseases	hepatic fibrosis	AKT, mTOR and p70S6K	energy sensor	activation	TGFβ1-simulated phosphorylation of AKT(downregulate0	(Domitrović et al., 2009;Panahi et al., 2018;Wan and Jiang, 2018)
Morin	microsomal lipid peroxidation	Fatty liver disease	COX-2 and iNOS	inflammatory mediators	inhibition	NF-κB (downregulation)	(Fang et al., 2003;Shankari et al., 2010)
Naringenin	HIV-1/HCV co-infective liver disease	HCV-mediated hepatocellular	ACSL4, GNMT, IFI27, and miR122		downregulation	NF-ƙβ (down regulate)	(Jain et al., 2011) (Hernández-Aquino and Muriel, 2018)
		carcinoma (HCC)				TNF-α (down regulate)	(Hernández-Aquino and Muriel, 2018)
Nobiletin	chronic inflammatory liver disease	liver cancer	PPARα and PGC1α		inhibiting adhesion,		(Kim et al., 2017) (He et al., 2016) (Wu et al., 2018)
	chronic inflammatory liver disease	liver cancer	ERK and PI3K/Akt	metastasis mediators	invasion, and migration	iNOS and COX-2, TNF-α (down regulate)	(Yuk et al., 2018)
Prunetin	lipid accumulation in the liver	Hyperlipidemia	AMPK	metastasis mediators	activation	HMG-CoA R (inactivates)	(Wei et al., 2018)

	adipogenesis in the liver	Fatty liver disease	PPARγ, C/EBPα, SREBP, aP2,	adipogenic genes	inhibition	LDLR (promote expression)	(Chen et al., 1998;Ding et al., 2016)
			LPL adiponectin, and leptin				(Zhang et al., 2007)
	adipogenesis in the liver	Fatty liver disease	SREBP, PPARγ, LXR, and HMG-CoA	lipid metabolism-related genes	suppressed	LDLR (promote expression)	(Walle, 2007)
	adipogenesis in the liver	Fatty liver disease	adipoR1, adipoR2	adiponectin receptors	induction	AMPK induction	(Wei et al., 2018)
Quercetin			iNOS, COX-2 and CRP protein level	inflammatory mediators	downregulation	NF-ƙβ (down regulate)	(Kumar et al., 2016) (Gupta et al., 2010)
Rutin	hepatic diseases	Hepatocarcinoma	PPARα, AMPK activity,	metastasis mediators	downregulation	SREBP-1(down regulate)	(Pan et al., 2014)
		fatty liver disease					
		obesity					
		hyperlipidemia					
	hepatic diseases	Hepatocarcinoma	p53 and CYP 2E1	reactive metabolic	downregulation	ROS (down regulate)	(Mansour et al., 2017;Nazeri et al., 2017)
		fatty liver disease		trichloromethyl radicals			
		liver cirrhosis		trichloromethyl radicals			
Silibin	microsomal lipid peroxidation	Fatty liver disease	COX-2 and iNOS	inflammatory mediators	inhibition	NF-κB (downregulation)	(YU and REN, 2008;Hernandez-Rodas et al., 2015)Younossi et al., 2017
Silymarin	hepatic centrilobular necrosis	paracetamol toxicity	glutathione reductase (GSH)	antioxidant enzymes	increase	microsomal ethanol-oxidizing system(increase)	(Lieber et al., 2003;Ni and Wang, 2016;Abenavoli et al., 2018)
		steatohepatitis, hepatic fibrosis					(Boari et al., 1981;Pradhan and

							Girish, 2006;Vargas-Mendoza et al., 2014)
	Steatosis	chronic hepatitis C	COX-2 and iNOS	inflammatory mediators	inhibition	NF-κB and AP-1 (downregulation)	(Saller et al., 2001;Jose et al., 2011)
Tangeretin	chronic inflammatory liver disease	primary biliary cirrhosis	Pregnane X Receptor(PXR)	nuclear receptor gene	activation	NF-κβ (down regulate)	(Omar et al., 2016) (Di Carlo et al., 1999)
		Liver fibrosis				TNF-α (down regulate)	(Fracanzani et al., 2008)
Tricin	liver inflammation	liver cirrhosis	ERK1/2 and Akt	downstream signaling molecules	supress	blocking cell cycle progression	(Arulselvan et al., 2016)(Seki et al., 2012)
	hepatic diseases	hepatocellular carcinoma	(PDGF)-BB	platelet-derived growth factor	inhibition	blocking cell cycle progression	(Malvicini et al., 2018)

Apiginin: Apigenin, a plant flavone, can improve hepatic health during severe liver disease conditions by down-regulating Nrf2-signalling and up-regulatingBCL-2 apoptotic pathway (Tsaroucha et al., 2016)

Caffeic acid: It is chemically 3,4-dihydroxycinnamic acid that occurs in the diet like fruits, green tea, wine, coffee bean components. Caffeic acid showed potential antioxidant and anti-inflammatory properties and is effective in treating major liver hitches(Kim et al., 2018). It can modulate the expression of kelch-like ECH-associated protein-1(Keap1), a hepatic carcinoma factor, by interacting with Nrf2 binding site and restraining it from binding to Keap1 and elevating the expressions of vital antioxidative signals like HO-1(Yang et al., 2017).

Catechin: Catechin from green tea extracts, selective seeds and fruits. It is categorized by the presence of a hydroxyl moiety at C3, C5 and C7 position of at A ring, and again in C3 and C4 of the B ring. Catechin with anti-hyperlipidemic property helps in treating diverse clinical condition associated with non-alcoholic fatty liver diseases where abnormality in protein and lipid metabolism plays the prime role in pathophysiology of the liver(Sun et al., 2015;Pezeshki et al., 2016).

Curcumin: It exerts its protective and therapeutic effects in oxidative coupled liver diseases by suppressing proinflammatory cytokines, lipid peroxidation products, hepatic stellate cells, and Akt activation. Curcumin ameliorates oxidative stress induced expression of Nrf2, SOD, CAT and GSH. Curcumin acts as a free-radical scavenger over the activity of different kinds of ROS via its active phenolic pharmacophore, β-diketone and methoxy group (Nabavi et al., 2014).

Epicatechin: It is a flavan-3-ol found in edible plant products like cocoa and other varieties of plant foods. Epicatechin plays an important role in lipid metabolism in fatty liver condition and hypercholesterimia(Cordero-Herrera et al., 2015). It can down-regulate important liver enzymes like SGPT and SGOT, which increases its liver anomalies(Shanmugam et al., 2017).

Ferulic acid: It is the most abundant phenolic acid in plants that has potent antioxidant ability to freeze the activity of the free radicals like NO, O_2^-. It exhibits prevailing anticholestatic action against liver cholestasis by inhibiting extracellular matrix related gene expression and also by disruption of the Smad signaling pathways and extracellular signal-regulated

kinases(Gerin et al., 2016). It sometimes activate the AMPK or the MAPK signaling pathway by enhancing lipid metabolism(Cheng et al., 2018). Several reports also confirmed the mode of action of ferulic acid is mediated by regulating the expression of several physiological factors viz; PPAR-α, CPT-1α towards lipid oxidation and this action is very important in treating with fatty liver diseases (Kim et al., 2011).

Hyperoside: It is a significant flavonoid that can fuel up the expression of diverse endogenous antioxidant enzymes and can quench free radicals formed during the metabolism of xenobiotics in the liver. Further, the capacity of hyperoside to regulate detoxifying enzymes phase II makes it potent as these enzymes are the prerequisite for liver during the initial round of oxidation. It helps in mitigating liver fibrosis by activating the Nrf2 signaling pathway, meant for neutralizing oxidants, when studied in CCl_4-induced hepatotoxicity (Wang et al., 2016;Xie et al., 2016;Zou et al., 2017).

Iccarin: It is reported from genus *Epimedium*and has been shown to delay the fibronectin and collagen accumulation in renal interstitial tissues and mesengial cells of rat model (Algandaby et al., 2017). Several published reports confirmed its protective role in inflammation blocking TNF-α and IFN-γ signalling pathway(Sinha et al., 2016).Other important protective actions of iccarin comprises of modulating expression of toll-like receptor and inhibition of the mitogen activated protein kinase (MAPK) (Mochizuki et al., 2002).

Magnolol: Magnolol from *Magnolia officinalis* is an important phenolic compound that maintains the oxidative balance during hepatotoxicity in galactosamine-injured mice models. Magnolin, another phenolics from same plant was reported to have ameliorating activity in lipid build up, insulin resistance and also in hepatic inflammation, when hepatocytes are exposed to free fatty acid *in vitro*(Tian et al., 2018).

Morin: Morin,a naturally occurring 2′,3,4′5,7-penta-hydroxyflavone, present in mulberry, tartary buckwheat, jackfruit, green tea, orange and in many dietary plants. It exerts beneficial effects on metabolism by suppressing canonical NF-Kβ signaling. (Caselli et al., 2016; Sinha et al., 2016).

Naringenin: Naringenin, a natural flavonoid, possesses antioxidant, anticancer and anti-inflammatory activity(Chtourou et al., 2015). Naringenin though exhibits very little antioxidant action directly as a scavenger, yet it helps inupregulating of Nrf2 pathway and thus uphold the normal

redox of the cell even in clinical conditions where prooxidants and reactive oxygens are formed as a of damage mechanism in hepatocytes ,(Esmaeili and Alilou, 2014).

Resveratol: Resveratrol, a 3,5,4′-trihydroxystilbene polyphenolic compound, is available in edible plants and selected fruits like grapes. It can control a specialized mammalian homolog, sirtuins (SIRT) (Andrade et al., 2014). Over expression of this homolog helps in treating non-alcoholic related fatty liver disease by regulation lipogenesis. Resveratrol is associated with considerable reduction in various liver enzymes, cytokines and also transcriptional factors like nuclear factor κB. It alleviates the nuclear factor-κB (NF-κB) expression following the stimulation of its inhibitor IκBα (Zhang et al., 2015b).

Wogoloside: It is another flavone that imparts hepatoprotective activity via different facilitating lipid metabolism by increasing oxidation process. AMPK signalling to bestow its effectiveness by various modules (Wang et al., 2015)

PLEASE INSERT FIGURE 12 HERE

Figure 12: gene-modelling showing various hepatic diseases and associated genes with it. A tool named Circus on shiny Circos server generated this image. *The blue band is showing various genes responsible for pathophysiological conditions, the green showing various hepatic complications and the red band shows the bioactive natural compounds possessive hepatoprotective activity. Various shades indicating the degree of relatedness between the various bands.*

Computational study for bioactive phenolic compounds

In silico appraisal presently happens to be a pronounced method of evaluation in various biological research these days. It has the benefit of low cost, fast execution, and the most constructive face of such study is to diminish the animal usage in various toxicity screening. PASS prediction assay (Lagunin et al., 2000) is highly studied these days which is based on primarily structure-activity relationships investigation of the training set that generally contains more than 200,000 compounds showing atleast not less than 3700 type of biological actions that interestingly allows to estimate if a phytochemical compound may have a particular effect (Dei et al., 2013). Lipinski's Rule of Five (Lipinski, 2004) is another method that can be applied to all the phenolic compounds to evaluate their drug likeness and pharmacological properties. Such information is very helpful in accessing the phenolic compounds to be a potential drug lead that can act as natural therapeutics. Only the compounds satisfying the Lipinski's criteria are further considered for further computational operations. Compounds that cleared the Lipinski's barrier were prepared for docking studies by their energy minimization in Marvin Sketch. Receptor-ligand interaction study using Hex docking tool (Macindoe et al., 2010) are also another mode of interaction study. Various amino acid of the target protein interaction with the lead compound are studied with respect to their bond length, bond angle. Hence, the reported phenolic compounds can thus be studied for good prospective of being used as medicine that targets various proteins for hepatic treatment. Reports of phosphorylated flavonoids i.e, iccartin is extensively studied for the potent target TGF-β where the score of molecular docking was reported 0.28 which was more than the marketed standard ursidiol 0.23 (Wheng et al., 2016).

Insilico studies have its implication in various pharmacological studies. From the initial protein, study to gene expression analysis related to any diseases can be carried out by the concept of pharmacogenomics. Phenolic compounds as hepatoprotective have been reported in the work of Kaveri et al., 2017, with *insilico* approach. The work was carried out on a group

of newly synthesized acetylated phenolics. A good number of target proteins of hepatic anomaly have been reported when target fishing was performed (Liu et al., 2017); which not only predicted the probable important target but directed the study of those prospective target in understanding the mechanism of that diseaseThis mode thus supports the traditional uses for hepatic disorders and thus can suggest major bioactive phenolic compounds as contributors to produce ethnopharmacological effect.

Future Prospects

Natural products and specially plant phenolics have become a promising therapeutic alternative and prospective replacement of conventional marketed drug in practice due to their effectiveness, minimal side effects and protective properties. Further, their dietary nature and availability is an add on and makes it all the reason to decline those generally available drugs that also cause toxicity to cells. Remarkable phenolics like curcumin and resveratrol are pharmacologically tested chemoprotective agent against treatment of hepatic carcinoma. Though widely held natural products evaluated until now are generally non-toxic in nature, yet a few studies on toxicity by certain natural products are also highlighted these days. As a result, appropriate selection of the natural based drug is also obligatory. All the important phenolics with their derivatives though studied and well reported for its immense therapeutic usage a few of compounds are not yet fully analyzed, as there are not enough studies available regarding them. Components of such compounds in the dieta varies with temperature and cultivation process. Furthermore, variation in the physicochemical properties could result from different mode of production of such plants, including agricultural and environmental factor. Many pharmacological reports have demonstrated that phenols has a variety of therapeutic effects, including anti-cancer, anti-diabetic, anti-obesity, immunomodulatory, cardioprotective, hepatoprotective and neuroprotective effects through antioxidant and anti-inflammatory activities. However, additional studies are required to understand biological functions and compositions of many phenolic viz; iccartin, morin in more detail. Understanding biological function, composition, and therapeutic effects could help preventing adverse effects from long-term administration of phenolic compounds, and developing health promoting properties. It is envisage from this presented review that plant based phenolics will not only reduce the risk of hepatopathy, but also will endow with an sure substitute towards various hepatotoxicity mediated diseases.

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Author Contributions Statement

Priyanka Saha(P.S): preparation of the initial draft and graphical representation for figures
Anupam Das Talukdar (A.D): finalizing the entire manuscript and supervising as a whole.
Rajat Nath(R.N): graphical repesentaion and undergoing various literature survey studies.
Jaggajit Sahu(J.S): gene network modelling and hgene expression study
Manabendra Dutta Choudhury(M.D): bioinformatics and phenolic sudy in hepatic disease
Satyajit D Sarker & Lutfun Nahar (SS): provided significant input into chemistry part of this review, editing and finalising the draft

Conflict of Interest Statement

The author declared to conflict of interest statement

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