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Phytochemicals as god gifted natural remedy against hepatic toxicity and cancer

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Abstract
Phytochemicals are the compounds that are produced by the plants via primary and secondary metabolism. Phytcohemicals are also called as 'Phytonutrients' because of their bioactive nature. Continuous tremendous hike in hepatic cancer and allopathic medicines induced side effects, turn researches towards the herbal therapy. Various phytoneutrients like curcumin, silymarin, resveratrol, Tanshinone IIA and EGCG possess potent biological activity against hepatic toxicity and cancer. Daily food products like spices i.e. turmeric, cinnamon, ginger, garlic, pepper, cereals and lentils, fruits like mangoes, apple, citrus fruits etc. are the rich sources of various types of anticancer compounds.

Keywords: Phytochemicals; Polyphenol; Anticancer compound; Hepatic cancer; Liver toxicity; Dietary sources

Introduction
Various herbal compounds have been isolated from numbers of medicinal plants that have been proven effective against Hepatic toxicity. Some important hepatoprotective drugs are Curcumin (diferuloylmethane), Resveratrol, Silibin or Silymarin and Tanshinone IIA. These compounds are isolated from their respective herbs i.e. Curcumin from *Curcuma aromatica*, Resveratrol, a polyphenol from the skin of red grapes, peanuts and berries, Silymarin, a flavonoid from Milk thistle plant and Tanshinone IIA, a diterpene which is isolated from *Salvia miltiorrhiza Bunge* [1].

Phytochemicals: as Antcancer Agents in Herbal Cancer Therapy
Natural products symbolize the richest source of chemical diversity that provides the basis for characterization of novel scaffold structures. Presently, the emergence of resistance to various cancer therapies makes natural products as a point of interest in a health care aspect. Herbal cancer therapy provides a safe, effective, cheap and alternate treatment to fight against cancer. Ayurveda, the traditional Indian medicinal system still uses herbal therapy for cancer treatment. There are around 460 species of medicinal plants that can be used as healer of various types of cancer. It is well understood that various measurements like pharmacognostical analysis, extraction procedure etc. are very crucial to obtained crude drug along with isolation of compound [2-7]. WHO reported that upto 80% world populations presently rely on traditional medicines for their primary health care [8]. Various phytochemicals act as scavengers whereas some are reported as cancer blocking agent [9, 10]. There are numbers of phytochemicals that possess anticancer activity. Some are as follows-

Polyphenols
Polyphenols is an important group of phytochemicals that categorized into Phenolic acids, flavonoids and stilbenes/lignans. Flavonoids are further divided into anthocyanins, flavones, flavonones, isoflavones and flavanols on the basis of their chemical structures. Flavanols are further categorized into catechins, epicatechins and proanthocyanindines [11, 12]. Phenolics provide protection against various external factors; act as phagostimulants and allelopathic agents in intra-plant relationship and also play crucial roles in antioxidant defense mechanism and U.V. absorption [13, 14, 15]. Phenolics also is the main component of human diet and research also suggested the inverse association between phenol rich diets and risk of various diseases like cancer, heart disease etc. [16]. Several phenolic compounds are now investigated that have potent chemo preventive, antioxidant and anticancerous activity; some are Epigallocatechin (EGCG), a component of Green tea, Resveratrol and Curcumin (Figure 1).

It is well reported that these compounds possess ability to modulate or activate Nrf2 gene (Nuclear factor-erythroid 2-related factor) that plays a crucial role in mediating ARE-dependent expression of genes [17]. Nrf2 is a major modulator of susceptibility of carcinogen-induced carcinogenesis [18]. Hsieh and Wu [19] reported cancer chemopreventive activity of Resveratrol in prostate cancer cells through apoptosis induction and cell growth inhibition. Curcumin, a yellow pigment of turmeric, possess antioxidant and anticancer activities against diethylnitrosamine induced hepatocarcinogenesis [20]. Polyphenols (a group of flavonoids, tannins and phenols) also contributes in defensive mechanisms by showing radical scavenging and antioxidant activities [21, 22].

Sulfur containing compounds (Organosulfur compounds)
Isothiocyanate compounds (ITCs)
Isothiocyanate compounds contain the R-N=C=S functional group. Brasicaceae and Fabaceae families are known to possess isothiocyanate compounds [23] and are formed from their corresponding precursors via enzymatic hydrolysis [24]. ITCs are found in cruciferous vegetables such as broccoli, Brussels sprouts, cauliflower and cabbage. Some ITCs are known to possess potent anticancer activity like Sulforaphane (SFN), phenethyl Isothiocyanate (PEITC) and Benzyl Isothiocyanate (BITC) (Figure 2) [25, 26]. Various reports suggested that ITCs are found to be effective against various numbers of cancers, including liver also [27-33]. SFN also has the ability to activate Nrf2 expression, results in obliterations in various biological pathways, thus proven to be an effective chemo-protective agent in various experimental models [34, 18].

- **Biological activity of ITCs**

Omar and Wabel [35] reported that ITCs possess potent ability to inhibit mutagenesis, DNA adduct formation, cell proliferation and tumor growth, modulation of enzyme activities, free radical scavenging activities. ITCs also showed anticarcinogenic activity, chemo-preventive activity and apoptosis induction [36-39]. ITCs have capability to modulate the GST (glutathione-S-transferase) enzyme activity that plays important role in carcinogen detoxification and CYP450. ITCs are also reported to stimulate GPx (Glutathione peroxidase), SOD (Superoxide dismutase) that helps in protection of cells from various ROS species [40]. Reicks and Crankshaw [41] reported that ITCs have the potential ability to decrease the activity of Cytochrome P4502E1 in the liver.

Diallyl sulfide (DAS; Figure 2)
DAS, a flavor compound, present in garlic bulbs. DAS may convert into diallyl sulfoxide (DASO) and diallylsulfone ($DASO_2$) by CYP450. These compounds have been shown to block phase I enzymes, but stimulate phase II enzymes in rat liver [42]. They have also showed protective role against lung cancer [43].

Indole-3-Carbinol (I-3-C; Figure 2)
I-3-C, a naturally occurring indole compound in various cruciferous vegetables has been shown to have pronounced anticancerous property against various chemically induced cancers which is attributed to change in various signaling pathways which regulates DNA repair, inflammation, cell division and growth, apoptosis and angiogenesis [44].

Dietary sources as anticancer agents
Various dietary sources like cereals, fruits, spices, edible fungi, etc. contain several compounds that are known to possess potent anti-hepatocarcinogenic activity. The detailed descriptions of some common dietary sources along with anticancer compounds are tabulated in Table 1.

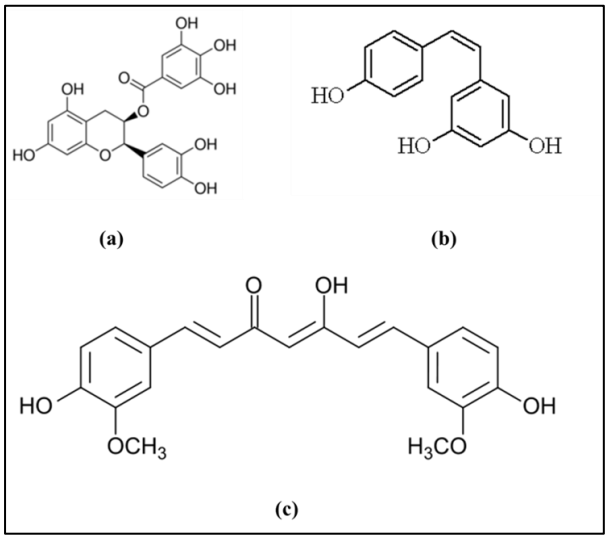

Fig 1: Chemical structure of various anticancer compounds (a) Epigallocatechin (EGCG) (b) Resveratrol (c) Curcumin

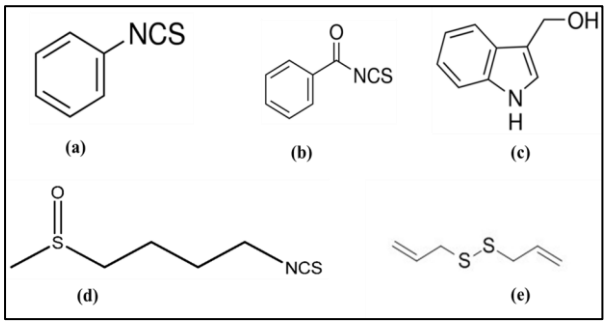

Fig 2: Chemical structure of various Sulfur containing compounds (a) Phenethyl Isothiocyanate (b) Benzyl isothiocyanate (c) Indole-3-Carbinol (d) Sulforaphane (e) Diallyl sulfide

Table 1: Dietary natural products that possess anti-hepatocarcinogenic activity

Natural products	Bioactive components	Bioactivities and possible mechanism	References
Fruits			
Pomegranate	Polyphenols	protecting against diethylnitrosamine induced hepatocarcinogenesis by suppressing oxidative stress and inflammatory response	[45, 46]
Apple	Polyphenols	inducing apoptosis, G2/M cell cycle arrest and inhibiting DNA topoisomerase II in cancer cells	[47]
Citrus fruit	Auraptene	suppressing tumor progression in N,N-diethylnitrosamine challenged rats by negative selection for cancer cells with -catenin mutation	[48]

Mango	Lupeol	ameliorating DMBA insult induced alterations in liver	[49]
Tomato	Tomatine	inducing antigen-specific cellular immunity and direct destructing cancer cell membranes	[50]
	Lycopene	protecting against chemical induced liver carcinogenesis through inducing apoptosis	[51, 52]
Mung bean sprouts	NA	increasing apoptosis, anti-tumor cytokines (TNF- and IFN-), IFN-production and upregulating cell-mediated immunity	[53]
Potato	Glycoalkaloids	selectively inhibiting cancer cell growth	[54]
Spices			
Garlic	Organo-sulphur compounds	inhibiting chemical induced DNA damage	[55]
	Sodium 2-propenyl thiosulfate	upregulating quinone reductase	[56]
	Allicin	inducing apoptosis through overproduction of ROS	[57]
	S-allylcysteine	inducing apoptosis and S phase arrest, inhibiting cancer cell migration and invasion	[56]
	aged garlic extract	inhibiting diethylnitrosamine induced preneoplastic lesions in liver	[58]
Turmeric	Curcumin	demonstrating anti-tumor activity against chemical induced hepatocarcinogenesis	[20]
	Sesquiterpe-noids	alleviating concanavalin A induced oxidative stress and inflammation, inhibiting cancer cell growth	[59]
	Aromatic tumerone	inducing apoptotic cell death via ROS-mediated ERK and JNK kinases activation	[60]
Ginger	Geraniol, Pinostrobin, Clavatol	inhibiting cancer cell proliferation though ROS-mediated apoptotic death	[61]
	6-shogaol, 6-gingerol	suppressing metastasis via down-regulation of MMP-9, urokinase-type plasminogen and up-regulation of TIMP-1	[62]
Pepper	Glycoprotein	preventing chemical induced liver carcinogenesis by immunomodulation and promotion of apoptosis	[63]
	Geranyl acetate, Citronella, Sabinene	increasing apoptotic cell death through ROS production	[64]
Cinnamon	Isoobtusilac-tone A	inducing apoptotic cancer cell death through overproduction of ROS	[65, 66]
Cereals			
Rice bran	Peptide hydrolysates, Phytic acid	inhibiting cancer cell growth	[67, 68]
Pigmented rice	Anthocyanin	promoting the cytotoxicity of vinblastine through a mitochondrial apoptosis pathway	[69]

Conclusion

On the basis of this study, it can be concluded that phytochemicals are the god gifted natural remedy to treat hepatic toxicity and cancer. Severe side effects of allopathic medicines in human body turned the mind of both researchers and peoples towards the herbal therapy or the use of plant derived bioactive compounds.

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Conflict of Interest

Authors stated that they have no conflict of interest.

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