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Hepato-Protective Activity and Pharmacological Study of Poly Herbal Tea Formulated From the Extracts of Selected Medicinal Plants Using Albino Rats

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ABSTRACT

The liver is the largest organ in human body that plays a major role in elimination of exogenous toxins (xenobiotics) and metabolism of drugs. Liver damage is a prevalent pathology that involves a variety of disorders including oxidative stress, steatosis, hepatitis, fibrosis, cirrhosis, apoptosis, and hepatocellular carcinoma.. Any diseases that affects the liver become major health problems and challenge health care professionals as well as the pharmaceutical industry. Because of the important roles of the liver in metabolism, secretion and storage, any injury to this organ can lead to transient changes in hepatic enzymes or life-threatening diseases like liver cirrhosis or liver failure. Modern drugs for liver disorders are either, not very effective, too expensive or not appropriate for chronic diseases because of their long term toxic effects. Hence there is increased interest in the use of herbal plants which includes; moringa oleifera, lemon grass, carica papaya leaf, scent leaf and ginger which are generally considered benign and are of particular value in the treatment of chronic diseases requiring prolonged therapy. The combine hepatoprotective potential of Poly-Herbal Methanol Extract (PHME) pretreatment against carbon tetra chloride (CCl_4)

carbon tetrachloride (0.6ml/kg) was administered as a 33% solution in paraffininduced hepatic damage in rats was investigated. Methanolic extract from the leaves of moringa oleifera, lemon grass, carica papaya leaf, scent leaf and rhizomes of ginger at a dose level of 50 mg kg^{-1} body weight as dose 1 and 100 mg kg^{-1} body weight as dose 2 was administered orally once for 14 days, prior to the administration of 0.6 ml of CCl_4 kg^{-1} body weight for 7 days. Serum markers such as Alkaline Phosphatase (ALP), Aspartate Transaminase (AST), and Alanine Transaminase were elevated prior to administration of CCl_4 and they were restored towards normalization in rats treated with the two doses of PHME the determination of rats' body weight and biochemical parameters such as serum urea and creatitine showed a remarkable decrease in rats treated with the doses of PHME when compare with those administered CCl_4 alone. Silymarin at a dose of 50 mg kg^{-1} was used as a standard reference also exhibited significant hepatoprotective activity against CCl_4 induced hepatotoxicity. The results of this study strongly indicate that PHME has got a potent hepatoprotective action against CCl_4 induced hepatic damage in rats.

Key words: Hepatoprotective, marker enzymes, poly-herbal methanolic extract, carbon tetrachloride

I. INTRODUCTION

The use of herbal medicine in the treatment of diseases is increasing worldwide. Indeed the effectiveness of some medicinal herbs in the treatment of diseases has been validated by rough research and clinical studies (Oguntola, 2007). Liver, an important organ actively involved in many metabolic functions, is the frequent target for number of toxicants (Meyer and Kulkami,

2001). The disorders associated with the organ are numerous and varied (Wolf, 1999). Serum or plasma enzyme levels have been employed as markers for monitoring chemically induced tissue damages (Hukkeri et al., 2002). Carbon tetrachloride is toxic to the liver and its toxicity is dose dependent and time of exposure (Junnila et al., 2000). In the liver, CCl_4 is metabolized in to the highly reactive trichloromethyl radical. The free radical generated would lead to auto oxidation of the fatty acids present in the cytoplasmic membrane phospholipids and cause functional and morphological changes in the cell membrane (Pandit et al., 2004).

In spite of tremendous strides in modern medicine, there are hardly any drugs that stimulate liver function and offer protection to the liver from the damage or help in the regeneration of hepatic sells (Guntupalli et al., 2006). In the absence of a reliable liver protective drug in the modern medicine, there are number of medicinal preparations recommended for the treatment of liver disorders (Chatterjee, 2000). A single drug cannot be effective against all types of severe liver diseases (Shahani, 1999). Therefore effective formulations have to be developed using indigenous medicinal plants, with proper pharmacological experiments and clinical trials.

With the above explanation, the Poly-Herbal Methanol Extract (PHME) made up of equal quantities of leaves moringa oleifera, lemon grass, carica papaya leaf, scent leaf and rhizomes of ginger were subjected to various assays in order to evaluate their hepatoprotective effect from mixture of these herbs against CCl_4 toxicity in albino rats.

Moringa is an outstanding source of nutritional component, its leaves (weight per weight) have the calcium equivalent of four times that of milk, the vitamin C content is seven times that of oranges, while its potassium is three times that of banana, three times the iron of spinach, four times the amount of vitamin A (which prevent night blindness) in carrots, and two times the protein in milk (kamal, 2008). Besides, moringa is also suggested as a variable supplement of dietary minerals. The pods and leaves of Moringa contains high amount of Ca, Mg, K, Mn, P, Zn, Na, Cu, and Fe (Aslam et al., 2005). Although, minerals content of Moringa shows variation in composition with changes in location (Anjorin et al., 2010). Aside from the mentioned nutritional value of Moringa leaves, it has also been reported to have the following medicinal properties, antitumor activity (Guevaraa et al., 1999), cardiac and circulatory stimulant i.e moringa oleifera leaf extract was reported as hypolipidimic, lowering body weight, heart weight, reduced serum cholesterol as tested in experimental animals (Guevaraa et al., 1999). Another study also reveals the leaf antiatherosclerotic, cardioprotective and hypolipidaemic effect (shah et al., 2011).

Papaya leaf has a numberless of benefits. In some parts of Asia, the young leaves of the papaya are steamed and eaten like Dengue fever Commencing on studies of Dr.Sanath Hettige, who conducted the research on 70 dengue fever patients, said papaya leaf juice helps increase white blood cells and platelets, normalizes clotting, and repairs the liver. Cancer Cell Growth Inhibition; Recent research on papaya leaf tea extract has demonstrated cancer cell growth inhibition. It appears to boost the production of key signaling molecules called Th1-type cytokines, which help regulate the immune system. Antimalarial and Antiplasmodial Activity; Papaya leaves are made into tea as a treatment for malaria. Antimalarial and antiplasmodial activity has been noted in some preparations of the plant, but the mechanism is not understood and not scientifically proven (Halim et al., 2011).Carica papaya leaves have been used in folk's medicine for centuries. Recent studies have shown its beneficial effect as an anti-inflammatory agent, for its wound healing properties, antitumor as well as immune-modulatory effects, rheumatoid arthritis, colon cancer, anti-sickling activity, prevent colon cancer, anticoagulant effect and as an antioxidant (Aravind et al., 2003), Antidiabetic activity, Antifertility effects, dengue fever treatment (Natarajan et al., 2014).

Cymbopogon, better known as lemon grass is a genus of Asian, African, and tropical island plants in the grass family (Soenarko, 1977).Lemon grass is an amazing super-herb that has been used for hundreds of years for both culinary and medicinal purposes. It is green and white, grass like plant with razor-like blades and it is grown across the planet in warm tropical climates. It is widely used as a cutlinary herb in Asian cuisine and also as medicinal herb in Indian. It has a subtle citrus flavor and can be dried and powdered, or used fresh. It is commonly used in teas, soups, and curries. It is often used as tea in African countries such as Togo and Democratic Republic of the Congo and Latin American countries such as Mexico. Research shows that lemon grasses have Healing properties and benefit and Ayurvedic properties.The primary chemical component in lemon grass is citral which has strong antimicrobial and anti-fungal properties, lemon grass inhibits microbial and bacterial growth in the body, both internally and externally, helping to prevent and cure bacterial infections in colon,

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stomach, urinary tract and respiratory system. Its leaves and stems are high in folic acid and essential vitamins such as pantothenic acid (vitamin B5), pyridoxine (vitamin B6) and thiamine (vitamin B1). Lemon grass also contains many antioxidant minerals and vitamins such as vitamin C, vitamin A. potassium, Zinc, Calcium, Iron, Manganese, Copper, and Magnesium. The tea can act as a diuretic and is highly effective in flushing toxins and waste out of the body; improving the function of many different organs including the liver, spleen and kidney. It can help to process fat more effectively. Lemon grass can also be used as calmative agent, to help in dealing with anxiety and nervousness (Carlini et al., 1986).

OCIMUM GRATISSIMUM also known as clove basil or African basil is native to Africa, Madagascar, Southern Asia, and the Bismarck Archipelago, and naturalized in Polynesia, Hawaii, Mexico, Panama, west Indices, Brazil, and Bolivia (Tsai et al., 2012).A polyherbal preparation of water extract obtained from the leaves of Gongronema latifolia, Vernonia amygdalina and ocimum gratissimum showed analgesic activity (Iroanya et al., 2009). The essential oil has potential for use as a food preservative, and is toxic to Leishmania (oliveira et al., 2009). Extracts of the leaves are documented to possess antidiabetic properties (Aguyi et al., 2000, Egesie et al., 2006, Owoyele et al., 2005) anti-hyperlipidemic effect (ayinla et al., 2011) and recently, it was shown to improve haematological variables in experimental diabetes mellitus via its well reported antioxidant property (Shittu et al., 2016).

GINGER (ZINGIBER OFFICINALE). This is a flowering plant whose rhizome, ginger root or simply ginger, is widely used as a spice or a folk medicine. It is an herbaceous perennial which grows annual stems about a meter tall bearing narrow green leaves and yellow flowers.

By definition, herbal tea alchemy and formulation is the synergistic brewing and blending of different herbal elements that work together to increase the nutritional components of the herbs being used. This is the basic concept of alchemy and the art of transforming one substance into another. Creating your own herbal tea formulation can be a very fun and instinctual process but does require a bit of practice and an intimate relationship with the herbs you are using. There are basically three parts to herbal tea preparation and design. Primary Herb that are major action herbs in the recipe that work directly on the "health focus" of your tea. Almost any herbs can be the primary ones with selections dependent on the specific goals you are trying to achieve. In addition, there can be more than one herb in this position, making up a total of 70-80% of the formula. Next is Supportive Herbs which is the nourishing herbs that build, sooth, fortify, tone and support the primary herbs in the recipe, working to harmonize and ease their delivery and effectiveness.As with the primary herbs, more than one herb can occupy this position which make up between 15-20% of the total tea ingredients used. These herbs are often soothing, buffering, nutritive and mucilaginous in nature. Lastly Activating herbs, used to activate, not only the body systems, but also the other herbs used in the tea recipe. They are referred to as catalysts or action herbs that stimulate, eliminate and get things moving. They make up between 10-15% of the total herbal tea preparation. These are diuretics, diaphoretics, laxatives, stimulants and warming herbs.A good herbal tea formula will include all three of these categories in the proper proportions (Atoui et al., 2005).

II. MATERIAL AND METHODS

Source of Plant Materials

Leaves of carica papaya, cymbopogon, ocium gratissium,moringa oleifera were obtained randomly from different gardens in Abeokuta, Ogun State, Nigeria and authentically by a botanist at Moshood Abiola Polytechnic, Abeokuta, Ogun State, Nigeria, while ginger rhizomes was purchased at Kuto Market, Abeokuta, Ogun State, Nigeria.

Experimental site

Instrumentation and chemistry laboratory of Science Laboratory Technology Department and pharmaceutical Department of Moshood Abiola Polytechnic, Abeokuta, Nigeria, were used and Federal university of Agriculture, Abeokuta, Nigeria central laboratory was used for other non-available instrumental analysis.

Extraction

The leaves of carica papaya (1kg), cymbopogon (1kg), ocium gratissium (1kg),and moringa oleifera(1kg) were washed, cut into small pieces and air dried for seven days. The samples were pulverized into fine powder. The purchased ginger rhizomes (1kg) was also sun dried for seven days and blended. Each quantities of the powder was passed through 40 mesh sieve, measure and mixed together. The 50g of the poly-herbal formulated tea was carefully added to the extraction thimble and defatted with 300ml of petroleum ether for 6 hours in a Soxhlet apparatus. The plant residue left after petroleum ether extraction was air dried and further extracted with 300ml methanol for three hours using the same

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procedure as above to obtain the methanol extract. The methanol extractions was done in triplicate using the same procedure. The combined methanol extracts obtained was dried under reduced pressure, and later kept in desiccators at room temperature until brittle, then weighed and stored in the refrigerator; weighed amount was dissolved in Tween-80 and used for the present investigation (Atawodi, 2011).

Animals

Thirty-five (35) Albino rats of male sex weighing about 150-200g were obtained. They were acclimatized for two weeks in a well-ventilated room temperature with natural 12+- 1 h day-night cycle in the propylene cages. They had free access to food and water before the commencement of the experiment. Food, but not water was withdrawn, 18hrs before commencement of experiments (Atawodi, 2011).

The rats were divided into seven groups with six animals in each group and were given dose as schedule:

Group A:Animals given a single administration of 0.15ml/kg body weight paraffin for 14 days. This group served as normal Control

Group B:Animals given CCl_4 only at a dose of 0.6 ml kg^{-1}as 33% solution (v/v) in paraffin daily for 7 days

Group C:Animals treated with 50 mg kg^{-1} of PHME daily for 14 days

Group D:Animals treated with 100 mg kg^{-1} of PHME daily for 14 days

Group E:Animals given CCl_4 and treated with 50 mg kg^{-1} of PHME daily for 14 days

Group F:Animals given CCl_4 and treated with 100 mg kg^{-1} of PHME daily for 14 days

Group D:Animals given CCl_4 and treated with 50 mg kg^{-1} of Silymarin in 2 % (v/v) aqueous paraffin daily for 14 days and this group serves as positive control.

On the 15th day the animals were sacrificed and various biochemical parameters were analyzed.

At the end of the experimental period animals were weighed and sacrificed by cervical decapitation under mild pentobarbitone anesthesia, blood was collected and the serum was separated by centrifuging at 3,000 rpm for 10 min, immediately after the sacrifice, the liver and the kidney were excised from the animals, washed in ice-cold saline. The biochemical parameters such as creatinine and urea concentration was determined by the method of Tarkang et al (2015) to analyze the effect of PHME on the kidney.

Marker Enzymes

The above collected serum was also used for the assay of marker enzymes. The Alkaline phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Transaminase (AST) were determined spectrophotometrically at 546nm as described by Reitman and Frankel (1957) using assay kits. Total protein concentration of the serum was determined using Biuret method, and utilizing bovine serum albumin as standard. (Atawodi, 2011).

Statistical Analysis

Values reported are the mean±SEM. The statistical analysis was carried out using Analysis of Variance (ANOVA) followed by Neuman-Keuls multiple comparison tests to identify the differences between treated groups and controls. The data was considered significant at $P < 0.05$.

III. RESULTS

Animal weight and Biochemical Parameters

In the present study a significant reduction in weight ($P < 0.05$) was observed in group B administered CCl_4 only when compared to group A that serves as normal control. Groups C and D treated with the two doses of PHME shows no significant difference when compared to the Group A(normal control). Group E and F shows significant different from group B but when compared with group G which was treated with the standard, it shows no significant difference. The result is as shown in table 1

Animal weight and Biochemical Parameters

Table 1: The average values of animals body weight under different experimental conditions

Groups	Weight in g
Baseline	150.24±2.62
Group A	165.20±3.23* NS
Group B	128.21±2.34*
Group C	167.35±4.62NS
Group D	145.45±3.56
Group E	138.35±4.53 NS

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Group F	140.51±3.56 ^{NS}
Group G	139.32±2.47 ^{NS}

Values are presented as mean ± standard error of mean (n = 6). Comparison between: a: Group A vs Group B, b: Group C and D vs Group A, c: Group G vs Group E and F. *p<0.05, NS: Not Significant

Table 2: Effects of PHME administration on alkaline phosphatase specific activity in ccl_4 induced Hepatic damage rats

Groups	serum (U/g protein)	Liver (U/g protein)	Kidney (U/g protein)
Baseline	2.49 ± 0.29^{a}	1.69 ± 0.13^{b}	8.46 ± 0.93^{b}
Group A	13.98 ± 0.46^{g}	1.74 ± 0.16^{b}	25.62 ± 3.24^{e}
Group B	21.67 ± 2.72^{h}	1.53 ± 0.15^{a}	12.94 ± 2.71^{c}
Group C	10.32 ± 1.51^{d}	1.74 ± 0.14^{b}	9.27 ± 1.85^{b}
Group D	11.87 ± 0.69^{def}	1.72 ± 0.18^{b}	13.33 ± 0.16^{c}
Group E	12.72 ± 0.70^{efg}	1.73 ± 0.13^{ab}	15.20 ± 1.37^{c}
Group F	8.31 ± 0.87^{c}	1.87 ± 0.16^{b}	8.15 ± 0.84^{b}
Group G	7.97 ± 0.57^{bc}	1.66 ± 0.15^{ab}	15.65 ± 2.33^{c}

Values are presented as mean ± standard error of mean (n = 6). Values with different letters down the column are significantly different at $p < 0.05$. silymarin = standard drug

Table 3: Effects of PHME administration on aspartate transaminase specific activity in ccl_4 induced Hepatic damage rats

Groups	serum (U/g protein)	Liver (U/g protein)	Kidney (U/g protein)
Baseline	2.89 ± 0.27^{a}	7.28 ± 0.13^{bc}	10.10 ± 0.81^{bc}
Group A	11.99 ± 0.69^{bc}	7.39 ± 0.79^{c}	15.76 ± 0.86^{ef}
Group B	18.26 ± 1.24^{d}	2.59 ± 0.15^{ab}	4.74 ± 0.78^{a}
Group C	11.79 ± 0.33^{bc}	7.72 ± 0.65^{c}	9.87 ± 1.45^{bc}
Group D	11.40 ± 0.47^{bc}	7.98 ± 0.95^{c}	9.84 ± 0.52^{bc}
Group E	10.12 ± 1.36^{bc}	5.72 ± 1.75^{c}	12.45 ± 0.03^{cde}
Group F	9.78 ± 1.75^{b}	7.54 ± 1.46^{c}	10.73 ± 0.89^{bcd}
Group G	11.97 ± 1.63^{bc}	7.94 ± 0.65^{c}	10.57 ± 1.12^{bcd}

Values are presented as mean ± standard error of mean (n = 6). Values with different letters down the column are significantly different at $p < 0.05$, silymarin (standard drug)

Table 4: Effects of PHME administration on alanine transaminase specific activity in ccl_4 induced Hepatic damage

	Serum (U/g protein)	Liver (U/g protein)	Kidney (U/g protein)
Baseline	1.85 ± 0.08^{f}	1.97 ± 0.09^{c}	1.83 ± 0.25^{c}
Group A	1.74 ± 0.19^{a}	3.45 ± 0.92^{c}	8.42 ± 0.42^{fg}
Group B	5.14 ± 0.39^{g}	1.23 ± 0.07^{a}	0.49 ± 0.14^{a}
Group C	2.14 ± 0.12^{de}	2.03 ± 0.25^{c}	2.94 ± 0.60^{d}
Group D	2.46 ± 0.18^{e}	3.45 ± 0.72^{cde}	3.54 ± 0.23^{d}
Group E	0.85 ± 0.14^{cde}	3.12 ± 0.13^{cd}	4.28 ± 0.63^{d}
Group F	1.21 ± 0.16^{bc}	4.14 ± 0.51^{e}	3.25 ± 0.84^{d}
Group G	1.89 ± 0.18^{de}	3.01 ± 0.16^{cd}	3.12 ± 0.27^{cd}

Values are presented as mean ± standard error of mean (n = 6). Values with different letters down the column are significantly different at $p < 0.05$

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Table 5: Effects of PHME administration on urea concentration in ccl_4 induced Hepatic damage rats

Groups	serum (mg/dl)	Kidney (mg/g tissue)
Baseline	**29.48 ± 0.73^{a}**	**2.81 ± 0.31^{b}**
Group A	**62.33 ± 2.40^{c}**	**3.37 ± 0.61^{d}**
Group B	**75.19 ± 104.68^{e}**	**3.92 ± 0.86^{b}**
Group C	**44.47 ± 15.37^{b}**	**6.94 ± 1.24^{d}**
Group D	**58 ± 28.76^{c}**	**4.32 ± 0.62^{bc}**
Group E	**77.21 ± 39.86^{d}**	**6.85 ± 1.75^{d}**
Group F	**68.74 ± 24.17^{d}**	**6.23 ± 0.84^{d}**
Group G	**32.05 ± 17.84^{c}**	**5.63 ± 0.51^{d}**

Values are presented as mean ± standard error of mean (n = 6). Values with different letters down the column are significantly different at $p < 0.05$. silymarin = standard drug

Table 6: Effects of PHME administration on creatinine concentration in ccl_4 induced Hepatic damage rats

Groups	serum (mg/dl)	Kidney (mg/g tissue)
Baseline	**0.67 ± 0.02^{b}**	**32.48 ± 4.68^{cde}**
Group A	**0.37 ±0.71^{b}**	**36.70±1.04^{cdef}**
Group B	**0.91 ±0.09^{e}**	**13.45 ± 1.82^{ab}**
Group C	**0.455 ±0.07^{b}**	**30.25±1.64^{bcd}**
Group D	**0.345 ±0.12^{b}**	**66.5±4.65^{g}**
Group E	**0.42 ±0.25^{b}**	**49.7 ±1.83^{cdef}**
Group F	**0.36 ±0.33^{ab}**	**75.48 ±5.64^{fg}**
Group G	**0.47 ±0.26^{ab}**	**45.82± 1.48^{c}**

Values are presented as mean ± standard error of mean (n = 6). Values with different letters down the column are significantly different at $p < 0.05$. silymarin = standard drug

IV. DISCUSSION

Table 2-6 show the effect of PHME on the activities of serum ALT, ALP, AST, urea and creatinine in CCl_4 induced liver damage in rat. The significant increase ($p < 0.05$) observed in the level of total protein concentrations and the activities of alanine aminotransferase, aspartate aminotranferase, and alkaline phosphatase in the serum when compared with controls which received distilled water only (p.o) indicates hepatotoxicity in the rat. CCl4 is one common hepatotoxin used in the experimental study of liver diseases (Obi et al., 1998; Ulicna et al., 2003). This might be due to the leakage from the cells through peroxidative damage of the membrane (Li et al., 2010).

The high level of the activities of marker enzymes observed in the serum of the ccl4-induced rats could have been due to the release of cellular enzymes as a response to CCl_4 administration which reflects a nonspecific alteration in the plasma membrane integrity and/or permeability and effect of the extract in reducing the marker enzymes in the serum and increasing it in the liver and kidney could be due to the presence of flavonoids in the formulated extract which have membrane-stabilizing properties (Sanz et al 1994).

The monitoring of the leakage of liver enzymes into the serum has proven to be a very useful tool in assessing liver damage (Nelson and Cox, 2000). The significant reduction ($p < 0.05$)

observed in the level of total protein concentrations and the activities of the transferases in the serum after simultaneous treatment of CCl_4 injection and administration of two different oral doses of 100 and 200 mg/kg of the formulated extract (Table 2-6) suggest that the extract must have protected the liver from the injurious effects of CCl4. This attribute might be as a result of the presence of some phytochemicals in the extract. Phytochemicals such as phenolics, flavonoids, alkaloids, saponins, carotenoids have been reported to have antioxidant properties capable of preventing hepatotoxicity that are associated with chronic diseases (Havsteen, 2002). Earlier an extract of Actaea racemosa with similar phytochemical components has been reported to possess hepatoprotective properties against CCl4 induced liver damage (Iniaghe et al., 2012). Renal disease is part of common complications of hepatic damage, in this present study, Table 5 and 6 shows the activities of urea and creatinine in the serum and kidney of the experimental animals. The significant increase in the levels of serum urea and creatinine (renal function markers) in untreated rats indicate signs of kidney dysfunctions in the hepatic damage rats (Verma and Bordia, 1998). Therefore, the increased urea and creatinine concentrations in the serum of ccl4-induced rats may be attributed to enhanced catabolism of both liver and plasma proteins that accompany glyconeogenesis (Khushk et al., 2010), treatment of the rats with formulated methanol extract at both dozes. The results were found comparable to silymarin. Silymarin that is composite name of three flavonoids isolated from milk thistle Silybum marinum and are used as hepatoprotectives against experimental hepatotoxicity of various chemicals including CCl_4 (Gadgoli and Mishra, 1999).

In conclusion the Poly-Herbal methanolic extract possesses protection against CCl_4 induced liver damage. The protections against liver damage by the PHME were found comparable to silymarin. Possible mechanism that may be responsible for the protection of CCl_4 induced liver damage by PHME may be that it could act as a free radical scavenger intercepting those radicals involved in CCl_4 metaboilism by microsomal enzymes. By trapping oxygen related free radicals the extract could hinder their interaction with polyunsaturated fatty acids and would abolish the enhancement of lipid peroxidative processes (Upadhyay et al., 2001). Work is still ongoing to investigate the Non-enzymatic and Enzymatic properties of the Poly-herbal formulated tea extract.

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