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Clinical evaluation of the hepatoprotective effect of *Katuki* (*Picrorhiza kurroa* Royle ex Benth.) processed in *Guduchi* (*Tinospora cordifolia* Wild.) Miers in patients receiving lipid lowering drugs (Statins)

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The hypolipidaemic drugs have attracted considerable attention because of their potential to prevent cardiovascular disease by retarding the accelerated atherosclerosis in hyperlipidaemic individuals. Statins are the first choice drugs for primary hyperlipidaemias with raised LDL and total cholesterol levels, with or without raised triglycerides levels, as well as for secondary hypercholesterolemia. Statin therapy is commonly associated with liver damage in terms of elevated aminotransaminases. Simultaneous use of hepatotoxicity reducing formulation is desirable for successful continuation of HMG-CoA reductase inhibitor (statins) over a desired period in hyperlipidaemic patients. So, the present clinical study was planned to evaluate the hepatoprotective effect of *Katuki (Picrorhiza kurroa* Royle ex Benth.) processed in *Guduchi [Tinospora cordifolia* (Wild.) Miers], on scientific parameters. In the present clinical trial, two groups of patients receiving standardized lipid lowering drug (Atrorvastatin 20 mg, twice daily) have been studied to evaluate the hepatoprotective effect of these drugs. The first group was given 2 gm of *Katuki* processed in *Guduchi*, twice daily with statin therapy. The second group was given 500 mg of starch powder filled in capsules, twice daily with statin therapy. The trial was conducted for three months and liver functions test were periodically evaluated to assess the hepatoprotective effect of drugs under trial. At the end of the trial, trial group exhibited its hepatoprotective efficiency over the control.

Keywords: Drug induced hepatitis, Ayurveda, Hepatoprotective effect, *Katuki, Guduchi,* Statins

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Cardiovascular diseases are the major contributor to the global burden of disease among the non communicable diseases. As per World Health Organization one third of all global deaths (15.3 million) are due to cardiovascular diseases. Dyslipidaemia is the one aspect of Pathophysiology that accounts for increased cardiovascular risk. Statins (HMG-CoA reductase inhibitor), the current treatment standard, have proven to be highly efficious in lowering low density lipoproteins cholesterol (LDL-C) and reducing coronary heart disease (CHD) risk[1]. The use of statins is associated with biochemical abnormalities of liver functions[2]. The HMG-CoA reductase inhibitor- associated elevation in liver enzymes resolves after discontinuation of the medication[3]. But the importance of lipid lowering drugs does not allow us to stop the use of these drugs for the betterment of the patient, hence, there is always need for simultaneous use of some drugs to reduce the hepatotoxicity of these drugs. Simultaneous use of hepatotoxicity reducing formulation is desirable for successful continuation of HMG-CoA reductase inhibitor (statins) over a desired period in dyslipidaemic patients. Drug induced hepatitis and its complications still do not have appropriate drugs in modern medicine. Patients of drug induced hepatitis may present with similar pathophysiology and clinical features to that of *Kosthashakhasrita Kamala* mentioned in Ayurvedic treaties[4]. Ayurveda in its herbarium has a lot of hepatoprotective herbs which can fill up this gap. Hepatoprotective herbal drugs like *Guduchi* [*Tinospora cordifolia* (Wild.) Miers], *Bhumyamalki* (*Phyllanthus fraternus* Webster), *Katuki* (*Picrorhiza kurroa* Royle ex Benth.), *Daruharidra* (*Berberis aristata* DC.), *Kalmegha* (*Andrographis paniculata*

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Wall .ex Nees) and *Bhringraja* (*Eclipta alba* Linn.), etc. have been suggested to be useful in hepatitis[5]. In the present clinical trial, drugs *Katuki* (*Picrorhiza kurroa* Royle ex Benth.) and *Guduchi* (*Tinospora cordifolia* Wild.) are selected as hepatoprotective drugs to protect liver parenchyma from hepatotoxicity caused by statins. Both the selected trial drugs are bitter, and are considered hepatoprotective and immunomodulators. In Ayurvedic literature, *Katuki* is considered *Tikta* (bitter) in *Rasa, Laghu* (light)*, Ruksha* (dry) in *Guna, Shita* (cold) in *Veerya, Katu* (pungent) in *Vipaka* and pacifies *Kapha* and *Pitta Dosha*. *Guduchi* is considered *Tikta* (bitter), *Kashaya* (Astringent) in *Rasa, Guru* (heavy), *Snigdha* (unctuous) in *Guna, Ushna* (hot) in *Veerya, Madhura* (sweet) in *Vipaka* and pacifies *Tridosha*[6]. Both of drugs are *Yakrituttejaka, Deepan, Kamalarogahara* and *Yakrit Vikarahara* and thus protect liver damage[7].

Methodology

The present clinical research was undertaken at Department of Medicine, Desh Bhagat Ayurvedic College & Hospital, Amloh, District Fatehgarh Sahib, Punjab. All the dyslipidaemic patients receiving of hypolipidaemic drug Atorvastatin (20 mg, twice daily) of either sex between the age of 30-60 yrs of rural and urban areas were potential trial patients. They were confirmed to have normal serum bilirubin, AST (SGOT), ALT (SGPT), serum alkaline phosphatase (ALP), and were not on any other hepatoprotective or hepatotoxic drug at the initiation of trial. Assessment of result therapy was made in different parameters in subjective parameters (chief complaints and associated symptoms and signs) and biochemical parameters (objective parameters). Each patient was subjected to series of laboratory tests such as serum bilirubin, AST (SGOT), ALT (SGPT), serum alkaline phosphatase (ALP), and liver ultrasound before treatment, after 15 days of treatment for 3 months of treatment to know the extent of liver damage as well as the rate of response to trial drugs. The trial was conducted for 3 months. Fresh raw drugs were procured from market. After botanical identification from the Department of Pharmacognosy (*Dravyaguna*), tablets of drugs were got prepared from hospital pharmacy. The standard of purify, quality and packing was maintained as per good manufacturing practice.

Trial group – In addition to tablet of Atorvastatin 20 mg twice daily, the patients of this group were given 2 gm of *Katuki* processed in *Guduchi* twice daily for 3 months. In this group 32 patients were registered, of which 25 completed full course of trial of 3 months.

Control group – In addition to tablet of Atorvastatin 20 mg twice daily, the patients of this group were given 500 mg of starch powder filled in capsules, twice daily for 3 months. In this group (control group), 36 patients were registered of which 25 patients completed full duration of trial.

Results

For evaluation of hepatoprotective effect of *Kutuki* (*Picrorhiza kurroa* Royle ex Benth.) processed in *Guduchi* [*Tinospora cordifolia* (Wild.) Miers], after use of 3 months in patients receiving statins, both subjective and objective evaluation criteria were applied. The reliable amongst them was liver function test including serum bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase (ALP). The trial patients were randomly scattered over the two groups, but administration of trial drugs and results were monitored from time to time. The observation regarding liver function tests of the patients over the trial are given (Tables 1-4). In the control group, there was a significant increase in ($p<0.05$) in the mean values total bilirubin from 0.84 mg/dl to 1.05 mg/dl (Table 1), AST (SGOT) from 37.05 IU/L to 74.55 IU/L (Table 2), ALT (SGPT) from 39.2 IU/L to 85.70 IU/L, (Table 3), and serum alkaline phosphatase (ALP) from 117.8 IU/L to 138.05 IU/L (Table 4). Whereas in trial group, there was a non significant ($p>0.05$) increase in the mean values of total bilirubin from 0.89 mg/dl to 0.92 mg/dl (Table 1), AST (SGOT) from 36.15 IU/L to 37.40 IU/L (Table 2), ALT (SGPT) from 38.25 IU/L to 41.25 IU/L,

Table 1 – Effects of drugs on total serum bilirubin in the patients receiving statin therapy

Groups	Serum bilirubin (Mean score) in mg/dl		Mean differ	SD±	SE±	%age ↑ in serum bilirubin	t	p
	BT	AT						
Trial Group	0.89	0.92	0.034↑	0.09	0.02	03.82	1.5	>0.05
Control Group	0.84	1.00	0.20↑	0.20	0.04	23.80	4.3	<0.01

Table 2 – Effects of drugs on AST (SGOT) in the patients receiving statin therapy

Groups	AST (SGOT) Mean score in IU/L		Mean differ	SD±	SE ±	%age ↑ in AST (SGOT)	t	p
	BT	AT						
Trial Group	36.15	37.40	01.25↑	06.18	1.38	03.45	0.9	>0.05
Control Group	37.00	74.55	35.5↑	40.72	9.10	95.90	4.1	<0.01

Table 3 – Effects of drugs on ALT (SGPT) in the patients receiving statin therapy

Groups	ALT (SGPT) Mean score in IU/L		Mean differ	SD±	SE ±	%age ↑ in ALT (SGPT)	t	p
	BT	AT						
Trial Group	38.25	41.25	03.0↑	07.64	1.70	07.84	1.7	>0.05
Control Group	39.20	85.7	46.5↑	41.44	9.26	118.00	5.0	<0.001

Table 4 – Effects of drugs on alkaline phosphatase in the patients receiving statin therapy

Groups	Serum alkaline phosphatase (ALP) Mean score in IU/L		Mean differ	SD±	SE±	%age ↑ in S. alkaline phosphatase (ALP)	t	p
	BT	AT						
Trial Group	117.4	124.15	06.75↑	16.93	3.78	05.74	1.7	>0.05
Control Group	117.8	138.00	20.25↑	24.08	5.38	17.19	3.7	<0.05

(Table 3), and serum alkaline phosphatase (ALP) from 117.4 IU/L to 124.15 IU/L (Table 4).

There were no significant differences between the both groups in terms of physical examination like icterus (jaundice), skin, liver size, weight, temperature , weight , general state and subjective features nausea , vomiting , loss of appetite, coating of the tongue and pain, and discomfort in the right hypochondrium. No significant differences were noticed in other haematological parameters between both the groups.

Discussion

The liver is an important organ for metabolizing and detoxifying drugs. The association between chemical and liver injury has been recognized since antiquity. There are a huge number of drugs and other chemicals that can produce hepatic injury. Drugs and their metabolites can damage the liver. Lipid lowering drugs especially statins (Atorvastatin, Simvastatin, Lovastatins & Fluvaststin, etc.) can cause or have been associated with an elevation in the liver enzymes (serum bilirubin, AST, ALT, serum alkaline phosphatase, etc.), indicating liver toxicity. The majority of liver abnormalities generally appear within the first 3 months of therapy and this abnormality is dose dependent. The pattern of hepatic injury from statins is typically hepatocellular or mixed in nature with rare instances of pure cholestatic picture. The proposed mechanisms of hepatotoxicity are varied depending on the drug or drug class, and include effect on the cytochrome P 450 system, impairment of bile acid transport proteins, immune mediated inflammatory response to the medication or its metabolites, immune mediated apoptosis by tumor necrosis factor, and oxidative stress due to intracellular damage. The most common adverse events associated with statins therapy are gastrointestinal disturbances, fatigue, localized pain and headache. Serious adverse events may include myopathy, elevated tansaminase levels and rhabdomyolysis. Hepatic failure rarely occurs with statin therapy and is an idiopathic event. The term “transaminitis” represents liver enzyme leakage without hepatotoxic consequences in patients receiving drug therapy of any kind.

The first biochemical sign of drug induced hepatitis is a rise in the concentration of AST (SGOT) and ALT (SGPT). These two enzymes which are normally present in the cell, are leaked into plasma, due to the damage of hepatocyte causing the drugs. In the next phase of development, the serum bilirubin content may go up. This symptom is caused due to the pressure of swollen liver cells on the finer ducts of bile, present within the liver (intrahepatic cholestasis). The present trial is exploration of ancient Ayurvedic

literature to screen and dose standardization of Ayurvedic herbal drugs in protecting the hepatic damage caused by drugs. The trial drugs showed definitive hepatoprotective effect over the trial period of 3 months. The trial drug *Katuki* is having potent hepatoprotective[8], immunomodulatory[9], antiinflammatory[10], antiviral, antioxidant[11], cholerectic[12], adaptogenic and membrane stabilizing properties and *Guduchi* is having potent immunomodulatory[13-14], hepatoprotective[15], antioxidant[16], anticancer[17], antineoplastic[18], antiallergic[19], antistress[20], antiulcer[21] activities, which are constitutive qualities for any hepatoprotective drugs to act against drug induced hepatitis. These activities have been attributed to their anticholestatic action, reduction in free radicals and reduction in cell protein necrosis as well as immune suppression and glutathione depletion reduction potential. The patients of trial group have not shown statistically increase in marker of enzymes of hepatotoxicity, i.e. serum bilirubin, AST (SGOT), ALT (SGPT) and serum alkaline phosphatase. On the other hand, patients of control group showed statistically increase in the markers of enzymes of hepatotoxicity. Patients of trial group exhibited its hepatoprotective efficiency over the control group.

Conclusion

In the present clinical trial, statins therapy was associated with liver damage in terms of markers of hepatotoxicity, i.e. elevation in serum bilirubin, AST (SGOT), ALT (SGPT), and serum alkaline phosphatase, but the clinically significant hepatotoxicity caused by statins remained absent. *Katuki (Picrorhiza kurroa* Royle ex Benth.) processed in *Guduchi (Tinospora cordifolia*) have proved to be effective hepatoprotective drug as both components have not produced statistically significant hepatotoxicity, i.e. elevation in serum bilirubin, AST (SGOT), ALT (SGPT) and serum alkaline phosphatase in the patients registered for the current trial. Thus, it can be concluded that *Katuki* (*Picrorhiza kurroa* Royle ex Benth.) processed in *Guduchi* (*Tinospora cordifolia*) are effective drugs in checking the progress of the drug induced hepatitis especially by statins.

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