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PHARMACOLOGICAL EVALUATION OF HEPATOPROTECTIVE ACTIVITY OF FRUITS EXTRACT OF SYZYGIUM AEORANTHUM

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ABSTRACT

Hepatotoxicity is a major side effect of synthetic drugs. It has important causes for the withdrawal and banning of most of drugs in the Pharmaceutical market. It is also a significant contributor of drug interactions on account of its playing a major role in the metabolism of drugs and other substances that enter the body. A significant amount of deaths occur due to diseases aggravated by the toxic action of therapeutic substances on the liver. There are not many measures to combat the hepatotoxicity of drugs except for reducing the dose, stopping the drug suspected to be responsible and changing the drugs substituting it with another drug of the same pharmacological action. Plant extracts have a wide range of medicinal actions, and throughout history, they have been used to treat many different types of diseases. In the treatment of many diseases, antioxidant therapy plays a key role, so current research is now directed towards finding naturally occurring hepatoprotective of plant origin. The medicinal properties of plant may be due to the presence of phytochemicals like tannins, flavonoids, terpenoids and steroids. Presently it has become a source of medicine for healing human and animal diseases. Hence, in order to contribute further to the knowledge of Indian traditional medicine, and its rich history. Hepatoprotective activity of hydroalcoholic extract of *Syzygium aeoranthum* fruits against Isoniazid-induced hepatic damage in Wistar albino rats was observed at two different doses, 200 and 400 mg/kg body weight. The healthy control, disease control, and standard drug *Silymarin*-treated groups were also maintained for the comparison. The liver marker enzymes SGOT, SGPT, ALKP, Serum Bilirubin and other metabolic parameters like total cholesterol, HDL-cholesterol were evaluated in all the experimental groups. The changes in liver function parameters were significant in comparison to disease control group and the observed efficacy was comparable to standard drug. The efficacy of hydroalcoholic extract of *Syzygium aeoranthum* fruits was found to be dose dependent. The histopathology study of liver also supports the presence of

hepatoprotective activity in *Syzygium aeoranthum* fruits by showing improved cytoarchitecture of liver cells in the treated groups.

Keyword: *Syzygium aeoranthum* fruits, Hepatotoxicity, phytochemicals

INTRODUCTION

The liver is the largest solid organ, the largest gland and one of the most vital organs that functions as a centre for metabolism of nutrients and excretion of waste metabolites. Its primary function is to control the flow and safety of substances absorbed from the digestive system before distribution of these substances to the systemic circulatory system. A total loss of liver function could leads to death within minutes, demonstrating the liver‘s great importance in view of this, this study was undertaken to review the physiology of the liver with a view to keep it functioning at its optimum and maintaining good health so as to avoid liver damages such as fatty liver, liver fibrosis and cirrhosis.

Liver diseases

Liver disorders are the most common health hazard found in developing countries due to dietary habits, alcohol ingestion, poor hygiene, unsupervised drug use and smoking etc. Liver diseases can be non-inflammatory, inflammatory and degenerative. High levels of plasma total cholesterol (LDL-C) and triacylglycerols (TGs) are associated with high risk of atherosclerosis and cardiovascular disease owing to the hepatic insufficiency. Any clinical defects or conditions which rise to impairment of liver are known as liver diseases. Liver diseases are mainly classified into two types: acute and chronic liver diseases. The acute liver disease occurs rapidly and usually exists for a very short duration. Chronic liver diseases are typically long term, generally over 6 months. In the clinical circumstances, the chronic disease causes periodical destruction and regeneration of liver parenchyma generates fibrosis and cirrhosis of the liver. Eventually, it causes an extensive degree of inflammation in the liver producing chronic hepatitis, cirrhosis, and liver carcinoma.

Hepatotoxicity

Hepatotoxicity implies chemical-driven liver damage. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g., microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins. More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. Chemicals often cause subclinical injury to liver which manifests only as abnormal liver enzyme tests. Drug induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures. More than 75% of cases of idiosyncratic drug reactions result in liver transplantation or death.

On the other hand, the majority of the hepatotoxicity agents damage hepatocytes and subsequently impair the kidney function mostly through lipid peroxidation or other oxidative forms. In cases of liver damage, the capacity of the natural antioxidant system is inadequate. ROS are generated by environmental causes such as Xrays, pollutants, ultraviolet radiation, or metabolic process in the mitochondria. The intracellular concentration of ROS

solely depends on the rate at which they are generated by exogenous or endogenous factors as well as their elimination by several endogenous antioxidants such as enzymatic and nonenzymatic processes.

Several reports have shown that oxidative stress triggered by free radicals is the main causative agent of liver damage such as degeneration, necrosis, swelling, and apoptosis of the hepatocytes. Liver injury or damage resulting from free radicals usually occurs via the mechanisms of lipid peroxidation and covalent binding with consequent tissue injury. ROS which include peroxyl, hydroxyl, alkoxy, and superoxide radicals destruct the membrane lipids, proteins, and nucleic acid, and this has also been linked to several aging related issues together with atherosclerosis, diabetes mellitus, lung and kidney damage, liver disorders, cancer, inflammatory diseases, and cardiovascular diseases. Lipid peroxidation interferes with cell membranes and consequently affects the structural integrity and functionality of the cell membrane that subsequently has a negative impact on the cell's potential to maintain constant ion gradients and transport. On the other hand, liver damage can also be caused by drug abuse at high dosages and certain chemicals.

2. MATERIALS AND METHODS

2.1 Plant material collection

Leaves of *Syzygium aeoranthum* were collected from local area of Bhopal in the month of September, 2021.Drying of fresh plant parts were carried out in sun but under the shade. Dried Leaves of *Syzygium aeoranthum*were preserved in plastic bags and closed tightly and powdered as per the requirements.

2.2 Extraction procedure

Fruits of *Syzygium aeoranthum* were shade dried at room temperature. The shade dried plant material was coarsely powdered and subjected to extraction with petroleum ether by maceration. The extraction was continued till the defatting of the material had taken place. 75 gm of dried powdered Leaves of *Syzygium aeoranthum*has been extracted with Hydroalcoholic solvents (Ethanol 80%) using maceration process for 48 hrs, filtered and dried using vacuum evaporator at 40^0C.

2.3 Determination of percentage yield

The percentage yield of each extract was calculated by using following formula:

$$\text{Percentage yield} = \frac{\text{Weight of Extract}}{\text{Weight of powder drug Taken}} \times 100$$

2.4 Phytochemical Screening

Phytochemical examinations were carried out for the extracts as per the standard methods. The *Syzygium aeoranthum* fruits extract acquire was subjected to the precursory phytochemical analysis following standard methods by Khandelwal and Kokate. The extract was screened to identify the presence of various active principles of alkaloids, glycosides, phenols, flavonoids, Terpenoids, Saponins, Steroids.

2.5 Total Phenolic content estimation

The total phenolic content of the extract was determined by the modified Folin-Ciocalteu method.

2.6 Total flavonoids content estimation

Determination of total flavonoids content was based on aluminium chloride method.

2.7 Isoniazid induced hepatoprotective activity of Leaves of *Syzygium aeoranthum*

Wistar rats (180–250 g) were group housed (n= 6) under a standard 12 h light/dark cycle and controlled conditions of temperature and humidity (25±2 °C, 55–65%). Rats received standard rodent chow and water *ad libitum*. Rats were acclimatized to laboratory conditions for 7 days before carrying out the experiments. All the experiments were carried in a noise-free room between 08.00 to 15.00 h. Separate group (n=6) of rats was used for each set of experiments. Animals were kept fasting providing only water, leaves of *Syzygium aeoranthum* (50,100,150,200,300 mg/kg/day) was administered orally for 4 days of six groups of rats (n=6) and the animals were kept under observation for mortality as well as any behavioral changes for evaluation of a possible hepatoprotective effect.

Experimental designs

Group –I: Normal control (Sterile distilled water ml/kg, p.o.)

Group –II: INH (Isoniazid) solutions were prepared in sterile distilled water (100 mg/kg, p.o.)

Group -III: *Syzygium aeoranthum* Extract (200mg/kg, p.o.) + INH (100 mg/kg, p.o.)

Group –IV: *Syzygium aeoranthum* Extract (400mg/kg, p.o.) + INH (200 mg/kg, p.o.)

Group –V: Silymarin (2.5 mg/kg, p.o.) + INH (100 mg/kg, p.o.)

RESULTS AND DISCUSSION

3.1 Result of Percentage Yield

The yield of extracts obtained from samples using hydroalcoholic as solvents are depicted in the table 3.1.

Table 3.1: % Yield of fruit extracts of *Syzygium aeoranthum*

S. No.	Solvents	% Yield
1.	Hydroalcoholic	9.76

3.2 Result of Phytochemical screening of extracts

Table 3.2: Phytochemical screening of extracts *of Syzygium aeoranthum*

S. No.	Constituents	Hydroalcoholic extract
1.	**Alkaloids**	
	Mayer's Test	+ve
	Wagner's Test	-ve
	Dragendroff's test	+ve
	Hager's test	+ve
2.	**Glycosides**	
	Modified Borntrager's Test	+ve

	Legal's test	+ve
3.	**Flavonoids**	
	Lead acetate	+ve
	Alkaline test	+ve
4.	**Phenolics**	
	Ferric Chloride Test	+ve
5.	**Proteins and Amino acids**	
	Xanthoproteic test	-ve
	Ninhydrin Test	-ve
6.	**Carbohydrates**	
	Molisch's Test	-ve
	Benedict's Test	-ve
	Fehling's test	-ve
7.	**Saponins**	
	Froth Test	+ve
	Foam test	+ve
8.	**Diterpins**	
	Copper acetate test	+ve

3.3 Results of estimation of total phenolic contents

Table 3.3: Total phenolic and total flavonoid content of *Syzygium aeoranthum* extract

S. No.	Extract	Total Phenol (mg/100mg)	Total flavonoid (mg/100mg)
1.	Hydroalcoholic fruits *extract of Syzygium aeoranthum*	1.031	1.585

3.4 Results of *In –Vivo* hepatoprotective activity of extract

Table 3.4: Effect of Hydroalcoholic extract of Total phenolic and total flavonoid content of *Syzygium aeoranthum* extract and Silymarin on % SGOT levels in Isoniazid induced hepatotoxicity in rats.

Treatment	Dose	SGOT (%)
Normal	1 ml/kg, p.o.	159 ± 2.5
INH	100 mg/kg, p.o.	330.62 ± 6.5
Syzygium aeoranthum Extract	200 mg/kg p.o.	217.0 ± 2.5***

Syzygium aeoranthum Extract	400 mg/kg p.o.	192.0 ± 2.9***
Silymarin	2.5 mg/kg p.o.	165.0 ± 2.6***

Table 3.5: Effect of Hydroalcoholic extract of *Syzygium aeoranthum* and Silymarin on % SGPT levels in Isoniazid induced hepatotoxicity in rats.

Treatment	Dose	SGPT (%)
Normal	1 ml/kg, p.o.	155.0 ± 2.50
INH	100 mg/kg, p.o.	320.0 ± 3.60
Syzygium aeoranthum Extract	200 mg/kg p.o.	202.0 ± 3.20***
Syzygium aeoranthum Extract	400 mg/kg p.o.	189.0 ± 3.40***
Silymarin	2.5 mg/kg p.o.	147.0 ± 3.70***

Table 3.6: Effect of *Syzygium aeoranthum* and Silymarin on % serum bilirubin levels in Isoniazid induced hepatotoxicity in rats.

Treatment	Dose	Serum Bilirubin (%)
Normal	1 ml/kg, p.o.	120.0 ± 4.50
INH	100 mg/kg, p.o.	276.0 ± 1.51
Syzygium aeoranthum Extract	200 mg/kg p.o.	161.0 ± 5.51***
Syzygium aeoranthum Extract	400 mg/kg p.o.	139.0 ± 3.60***
Silymarin	2.5 mg/kg p.o.	118.0 ± 2.50***

Table 3.7: Effect of *Syzygium aeoranthum* and Silymarin on % ALP levels in Isoniazid induced hepatotoxicity in rats.

Treatment	Dose	ALP (%)
Normal	1 ml/kg, p.o.	158.0 ± 3.20
INH	100 mg/kg, p.o.	315.0 ± 5.57
Syzygium aeoranthum Extract	200 mg/kg p.o.	221.0 ± 4.30***
Syzygium aeoranthum Extract	400 mg/kg p.o.	191.0 ± 3.78***
Silymarin	2.5 mg/kg p.o.	158.0 ± 5.40***

DISCUSSION

Syzygium aeoranthum are an important medicinal plant which is used in traditional medicine to treat many diseases. The liver may be considered as the most important organ in drug toxicity for two reasons: on the one hand it is functionally interposed between the site of absorption and the systemic circulation and is a major site of metabolism and elimination of foreign substances; but on the other hand these features also render it a preferred target for drug toxicity. Drug-induced liver injury therefore poses a major clinical problem. Liver plays a major role in detoxification and excretion of many endogenous and exogenous compounds, any injury or impairment of its function may lead to several implications on one's health. Management of liver diseases is still a challenge to modern medicine.

Increased in the level of activities of SGPT, SGOT and ALP in the blood reflect the damage of liver hepatocytes and indirectly impairment of liver functions following APAP-induced hepatotoxicity. In Table, SGPT, SGOT and ALP activities were significantly elevated ($p<0.05$) after administration of APAP. Treatments with 100 and 200 mg/ kg of *Syzygium aeoranthum* Fruits extract significantly reduced the elevation of these enzymes ($p<0.05$). The reduction of liver enzymes was seen to be to the level of the control group and it was also similar to the level of group pretreated with silymarin. One of the hallmark signs of hepatic injury or damage is apparent leakage of cellular enzymes into plasma. In addition, the extent and type of liver injury or damage can be accessed based on the presence or absence of specific enzymes in the blood stream. In general measurement of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase are commonly used as marker enzymes in accessing APAP induced hepatotoxicity. In this study, hepatoprotective effect of *Syzygium aeoranthum* Fruits is evidenced by the improvement SGPT, SGOT, ALP and serum bilirubin levels. Treatment with *Syzygium aeoranthum* Fruits extract suppresses Isoniazid induced SGPT, SGOT, ALP and serum bilirubin elevations. Previous studies have reported elevations of transaminases after Isoniazid-Rifampicin treatment. The increase is time dependent with significant elevation noted after 48 h ($p<0.05$) suggesting severe hepatocellular damage caused by leakage of these enzymes into circulation that is normally cytoplasmic in location.

Both the test groups i.e. low dose and high dose treated Groups shown dose dependent hepatoprotective activity. The test groups containing the plant extract alone showed an improvement in the liver activity. It clearly indicates that the plant "*Syszygium aeoranthum* Fruits" has the hepatoprotective activity. This study showed that

Syzygium aeoranthum Fruits has a significant protective action against the hepatotoxicity induced by the drugs used in the treatment of tuberculosis. The hepatoprotective role of *Syzygium aeoranthum* Fruits might be due to its antioxidant potential mechanism suggesting that the extract of plant may be useful to prevent the oxidative stress induced liver damage.

CONCLUSION

Natural products are playing a vital role in health care for decades. Often different sources of natural products, plants have been a source of chemical substance, which serves as drugs in their own right or key ingredients in formulation containing synthetic drugs. Herbal based therapeutics for liver disorders has been in use in India for a long time and has been popularized world over by leading pharmaceuticals. Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still unacceptable treatment modalities for liver diseases. The use of natural remedies for the treatment of liver diseases has a long history, starting with the Ayurvedic treatment, and extending to the Chinese, European and other systems of traditional medicines. A large number of plants and formulations have been claimed to have hepatoprotective activity. The present study concluded that the ethanolic extract of *Syzygium aeoranthum* Fruits may be used as an effective hepatoprotective agent. Further studies on isolation and structural determination of active principles might be worthy.

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