

# EVALUATION OF THE PROPHYLACTIC AND THE POSSIBLE THERAPEUTIC EFFECTS OF SILYMARIN IN EXPERIMENTAL LIVER CIRRHOSIS

*By*

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## INTRODUCTION

Silymarin is a substance which was isolated in 1968 from the seeds of the milk thistle (*Silybum marianum* L. Gaertn), a species known in antiquity as an efficacious and medicinal plant (wagner et al., 1968). The chemical structure of silymarin has been elucidated and satisfactorily defined. Silymarin with refined techniques of chemical separation was found to be formed of three compounds which are isomers and have the empirical formula  $C_{25}H_{22}O_{10}$  (wagner et al., 1974).

The pharmacological and clinical investigations proved that silymarin had a general protective action on the liver cells.

Silymarin was found to exert a

marked protective effect in different forms of liver damage e. g. carbon tetrachloride (Rauen and Schriewer, 1971 and Schriewer et al., 1973 a), ethanol (Castigli et al., 1977), ethioacetamide (Schriewer et al., 1973b) and thallium (Mourelle et al., 1988).

Although the value of the prophylactic use of silymarin is generally accepted, yet its use as a therapeutic agent in treatment of already formed hepatic damage is a point of controversy. Some authors denied its benefit (Hoefler et al., 1987), while others reported a pronounced therapeutic value of silymarin (Castigli et al., 1977 and Lapis et al., 1986).

The aim of present study was to evaluate the prophylactic versus the

possible therapeutic use of silymarin in experimental model of hepatic damage.

## MATERIAL AND METHODS

### Drugs Used :

- Sodium phenobarbitone powder (Alexandria - Co.).
- Carbon tetrachloride (Adwic - Co.) each 1 ml. contains 1gm. carbon tetrachloride.
- Silymarin (Legalon tablets, Madous - Co.) 35 mg. silymarin / tablet.

### Animals Used :

60 male albino rats, almost of the same age and weighing 80-110gm each were used throughout this study. They were caged under similar housing conditions, kept on a diet of milk and bread and were liberally supplied with water.

### Induction of Liver Cirrhosis in Rats :

Induction of liver cirrhosis was carried out according to the method described by Mclean et al., (1969) and Tamayo (1983). Sodium phenobarbitone was dissolved in tap water at a concentration of 0.4 gm/L. This was the only drinking water available to the rats in which induction of liver cirrhosis had to be carried out (Mclean et al.,

1969 and Proctor and Chatammara, 1982). This drinking water was given for one week before and one week after the first dose of carbon tetrachloride (CCL<sub>4</sub>). After these two weeks, the rats supplied by tap water for drinking until the end of the study. The animals were injected intraperitoneally with CCl<sub>4</sub> three times weekly for 10 weeks. Each rat received 0.1ml. in the first two weeks, 0.15ml. during the subsequent four weeks and 0.2 ml. for the remaining last four weeks.

Induction of liver cirrhosis was carried out into 45 rats and the remaining 15 rats were left as non cirrhotic control group (Group I). The cirrhotic rats were divided into three groups, each of 15 rats and were treated as follows:

- **Group (II) :** cirrhotic control group : Rats received no treatment and each rat was given 0.5ml. normal saline orally by gastric tube.
- **Group (III) :** Each animal was given silymarin 80 mg/kg (Paget and Barnes, 1964) daily throughout the CCL<sub>4</sub> treatment to produce cirrhosis (10 weeks).
- **Group (IV) :** Each rat was treated with silymarin in dose of 80 mg/kg/

day orally for 10 weeks after CCL<sub>4</sub> induction of liver cirrhosis was completed.

At the end of the study, animals were sacrificed, blood samples were collected and sera were separated for determination of serum glutamic pyruvic transaminase (SGPT) and glutamic oxalacetic transaminase (SGOT) according to Reitmain and Frankel method (1957), serum alkaline phosphatase (Belfield and Glodberg, 1971) serum bilirubin (Jendrassik, 1960), total cholesterol (Flegg 1973), triglycerides (Frings and Dunn, 1970) and free fatty acids (Duncombe, 1964).

The liver was carefully dissected and removed. The liver specimens were fixed in 10% neutral formalin, dehydrated, cleared and embeded in paraffin. Sections were cut at 5 U., stained with haematoxylin and eosin for histopathological examination.

## RESULTS

As illustrated in table (1), CCL<sub>4</sub> administration alone produced significant elevation of serum SGOT, SGPT, alkaline phosphatase, bilirubin, free fatty acids and significant fall of serum total cholesterol and triglyceride in comparison to non cirrhotic control group

( $P < 0.001$ ). Meanwhile the prophylactic use of silymarin in group (III) completely prevented these CCL<sub>4</sub> induced changes; since all the parameters estimated were more or less similar to control non cirrhotic group ( $P > 0.05$ ).

As shown in table (2) administration of silymarin to cirrhotic rats (Group IV) produced significant decrease in serum levels of SGOT, SGPT, alkaline phosphatase, bilirubin and free fatty acids and significant rise of serum triglycerides and total cholesterol in comparison to untreated cirrhotic group ( $P < 0.001$ ). However, most of these estimated parameters were still significantly different from the values observed in the non cirrhotic control group, i. e. the CCL<sub>4</sub> induced changes were partially but not completely corrected.

### Histopathological Findings :

#### Macroscopic Findings :

Most of the animals in group II (only CCL<sub>4</sub> treatment) and group IV (Silymarin therapy after CCL<sub>4</sub> treatment) showed fine nodular surface and firm consistency of the liver. Meanwhile, all animals of group I (control non treated) and most of the animals in group III (concurrent silymarin and CCL<sub>4</sub> treatment) showed

more or less normal appearance of liver.

#### Microscopic Findings :

The liver of control non treated group revealed normal lobular architecture without significant pathological changes (Fig. 1) On the other hand, ten out of fifteen rats in group II (Cirrhotic control, only CCL<sub>4</sub> treatment), showed picture of complete liver cirrhosis in the form of variable sized regenerating liver cells nodules surrounded by fibrous tissue heavily infiltrated by lymphocytes. The hepatocytes showed marked hydropic degeneration with ballooning and areas of necrosis, while portal tracts and central veins lost their regular spacing (Fig. 2). Focal areas of fatty change were present in some animals. Three of the remaining five rats showed picture of hepatitis with developing cirrhosis. The liver cells appeared swollen and have formed groups. The architecture was destroyed and curving septa extending from portal tracts between the groups of liver cells were noticed, (Fig. 3). The other two rats showed massive liver cell necrosis involving almost all liver cells in all lobules with only a few surviving periportal hepatocytes (Fig. 4).

In group III (concurrent silymarin and CCL<sub>4</sub> treatment) eleven out of fifteen rats had more or less normal livers with no significant pathological changes (Fig. 5). The remaining four rats showed the picture of cirrhosis, but however, it was of mild activity. The regenerating nodules were focally present with much decrease in the amount of surrounding stroma as well as of the lymphocytic infiltration. Only mild hydropic degeneration without necrosis of hepatocytes was observed (Fig. 6). On the other hand, in group IV which was treated with silymarin after induction of liver cirrhosis, nine rats out of fifteen showed the picture of complete cirrhosis, but of moderate degree of activity as the lymphocytic infiltration and the amount of stroma surrounding the regenerating nodules were slightly decreased than in the only CCL<sub>4</sub> treated group (Fig. 7). The remaining six rats showed histopathological lesions ranged from only necrotic changes to the picture of developing cirrhosis.

#### DISCUSSION

In the present study, long term administration of CCL<sub>4</sub> caused histopathological changes in rat's liver which were similar to cirrhosis in man. Similar findings were reported by De Heer



et al., (1980) and Tamayo (1983). These histopathological changes were accompanied with biochemical changes that indicated deterioration of liver functions including significant elevation of serum activities of SGOT, SGPT and alkaline phosphatase and the concentration of bilirubin and free fatty acids (F. F. A.) together with significant fall in serum total cholesterol and triglycerides. These biochemical changes were in agreement with those reported by schriewer et al., (1973a) and Mourelle et al., (1989).

Toxic injury of liver by CCL4 is actually the result of it's metabolic conversion by a complex of enzymes of the hepatocytes smooth endoplasmic reticulum to a highly reactive haloalkane (CCL3) and chloine (CL) free radicals. These free radicals react with molecular oxygen to form peroxides which can also serve as free radicals (Anderson & Kissane, 1977). All the formed free radicals in turn could interact with unstaturated fatty acids in lipid-containing cell membranes and organells causing peroxidation, which changes the physicochemical properties of the membrane lipids so that they can no longer maintain their biological functions (Zimmerman, 1978). This inevitably results in an outflow of

enzymes from hepatocytes with subsequent rise in serum SGOT, SGPT, and alkaline phosphatase activities, (Mac Sween et al., 1987).

Electron microscope studies had shown that CCL4 caused serious structural damage of endoplasmic reticulum and somewhat later of the mitochondria with subsequent impairment of their functions (Judah et al., 1970). The impairment of functions of endoplasmic reticulum should lead to diminution of protein synthesis including lipid acceptor proteins with subsequent accumulation of lipids in the liver as triglycerides, since these can be secreted from the liver into the blood only as lipoproteins (Schriewer et al., 1973 a and Schriewer & Lohmann, 1976). This could explain the reduction of serum total cholesterol, triglycerides and the fatty change of hepatocytes demonstrated in the present study following administration of CCL4. Mitochondrial injury disturbs their capacity to conserve energy by generation of ATP and loss of ion pumping function of the cell membrane. Therefore, the cell undergoes progressive swelling which starts in the early phase of CCL4 injury and later becomes more manifest when the cells lose their capacity to prevent

passive inward diffusion of sodium ions and water (Anderson & Kissane, 1977). This provides an explanation for hydropic degeneration with ballooned hepatocytes observed in the present study after CCL<sub>4</sub> administration. Mitochondria also lose other functions, among which is their capacity to oxidize fatty acids which may be still another mechanism leading to accumulation of lipid in hepatocytes and enhances the development of fatty changes (Schriewer & Lohmann, 1976 and Anderson & Kissane, 1977). This could also explain the increase of serum level of free fatty acids reported in the present study.

The CCL<sub>4</sub> degenerative changes of hepatocytes will result in cell death (necrosis) which with frequent repeated administration of CCL<sub>4</sub> progresses to cirrhosis due to long continued loss of liver cells, accompanied by replacement fibrosis infiltrated by lymphocytes and compensatory liver cell hyperplasia with regenerating nodule formation (Anderson, 1980).

In this study simultaneous silymarin administration during the time of induction of CCL<sub>4</sub> liver cirrhosis largely improved the histopathological changes since induction of cirrhosis was

prevented in most animals who had more or less normal livers and in the few rats who developed cirrhosis the fibrous tissue around the regenerating nodules as well as the lymphocytic infiltration were much less. At the same time the degenerative changes were less obvious and the liver cells necrosis was disappeared. Moreover, the biochemical abnormalities were completely normalised compared to the cirrhotic control (only CCL<sub>4</sub> treatment) group. These results confirm the earlier studies that demonstrated the prophylactic biochemical effect of silymarin in CCL<sub>4</sub> induced liver cirrhosis (Rauen & Schriewer, 1971 & 1973 and Schriewer et al., 1973 a, b). These findings could be explained by both lipotropic effect with diminution of toxic fatty change in the liver and necrotropic effect i. e. it prevents cell necrosis (Schriewer & Lohmann, 1976). Through these effect silymarin could prevent CCL<sub>4</sub> induced degenerative changes and limit the necrosis of hepatocytes and suppress the initiation of the hepatic cirrhosis.

The anti-hepatotoxic activity of silymarin against the lesions produced by CCL<sub>4</sub> was also evident when the drug was given after liver cirrhosis had occurred i. e. as therapeutic agent. The

rise in serum transaminases, alkaline phosphatase, bilirubin and free fatty acid and the fall in serum triglycerides and total cholesterol levels were significantly far less in animals treated with silymarin after CCL<sub>4</sub> than in controls given CCL<sub>4</sub> but not treated. Compared with the non cirrhotic animals, this improvement of the biochemical change although significant was not complete. Also, the histopathological changes were partially corrected in silymarin treated animals in the form of diminution of the amount of stroma surrounding the regenerating nodules and the accompanied lymphocytic infiltration as compared with cirrhotic control (Only CCL<sub>4</sub> treatment) group. However, silymarin did not completely reverse the picture of cirrhosis induced by CCL<sub>4</sub> and the improvement produced was not as much as that was observed in animals given silymarin prophylactically during CCL<sub>4</sub> administration. Although Hoefler et al. (1987) denied any therapeutic benefit of silymarin, its potential therapeutic value had been reported by many authors (Rauen & Schriewer, 1971; Castigli et al., 1977 and Lapis et al., 1986).

They reported that silymarin resulted in reduction of the amount of col-

lagen measured biochemically in extracts prepared from cirrhotic livers. In the present study based on histopathological assessment we also observed diminution of the amount of stroma around the regenerating nodules. In addition, these authors assumed that, in cases of toxic liver damage all the cells of the liver can be classified into three categories. Some are still intact, others are degenerated cells and others are necrotic. By its prophylactic action, silymarin can protect the intact cells i. e. prevent initiation of the process of the degenerative changes and hinder the development of liver cirrhosis at an early stage. By its therapeutic action, silymarin can reinvigorate the degenerated cells i. e. interrupts the loss of hepatocytes and retards the progress of cirrhotic changes. In the development of cirrhosis irregular liver cell hyperplasia and fibrosis interfere with blood flow to such an extent that, whatever the initial cause of injury, hepatocyte loss (necrosis) continues as a result of ischaemia and the cirrhotic changes become progressive and a vicious circle of necrosis (with subsequent cell hyperplasia and fibrosis) ischaemia necrosis set up (Anderson, 1980). Accordingly, silymarin which could reinvigorate the degenerated cells could prevent further

ischaemic necrosis, interrupts this vicious circle and diminishes the rate of progression of cirrhotic changes. This assumption is in agreement with the results of the present study where silymarin normalized the biochemical abnormalities and largely corrected the histopathological changes of CCL4 induced liver cirrhosis when given prophylactically and produced a partial but significant improvement when given therapeutically. This point is worthy to be considered in clinical use of silymarin as early as possible in treatment of any hepatic disease or on exposure of liver to any hepatotoxic agent.

The basic mechanisms of the hepatoprotective lipotropic and necrotropic effects of silymarin can be attributed to several factors viz : Silymarin largely restores the normal ultrastructure of hepatocytes. Electron microscope studies have shown that silymarin exerts demonstrable preventive and therapeutic effects on mitochondrial and endoplasmic reticulum damage produced by CCL4 (Themann, 1969). Silymarin direct protective action on the liver might be achieved by stabilization of intracellular organelles and cell membranes. The integrity of these cellular membranes maintain the met-

abolic, detoxicating and synthetic functions of the cells. (Vogel & Temme, 1969 and Muriel & Mourelle, 1990 a,b). This could explain, at least in part, how silymarin improved the biochemical as well as the histopathological changes induced by CCL4 in the present study.

The membrane stabilizing effect of silymarin can be attributed to reduced membrane phospholipid turnover and membrane lipid peroxidation due to some antioxidant properties of silymarin (Mourelle et al., 1988 and Muriel & Mourelle, 1990 a,b). The membrane lipid peroxidation in case of CCL4 toxicity is due to formation of highly reactive free radicals e. g. CCL3, CL and peroxides (Anderson & Kissane, 1977).

Silymarin by virtue of its capacity as a radical acceptor could prophylactically prevent lipid peroxidation and therapeutically inhibit it (Feher et al., 1989). Again, this could partly explain why silymarin has superior efficacy as a prophylactic than as a therapeutic agent in treatment of liver damage.

Several studies indicated that silymarin could intervene directly in cell metabolism not only through preserva-



tion of intracellular organelles but also acts at a nuclear level.

It stimulated the synthesis of ribosomal R. N. A. within the nucleus (Sonnenbichler et al., 1976).

Finally experimental and clinical evidences suggested that immunomodulatory activity of silymarin might be involved in the hepatoprotective action of the drug and improves the depressed immunoreactivity in cirrhosis (Lang et al., 1988 and Feher et al., 1989).

It could be concluded that, silymarin exerts both prophylactic and therapeutic effects in hepatic disorders. However, its prophylactic action is more superior to its therapeutic value. This point could stress the use of silymarin as early as possible in management of any liver disease or on exposure of liver to any hepatotoxic agent.

### SUMMARY

The present work was conducted to evaluate the prophylactic and possible therapeutic effects of silymarin in experimental liver cirrhosis. 60 albino rats were included in this study, they were divided into four equal groups.

The first group was non cirrhotic and served as control, the other three groups were rendered cirrhotic by intraperitoneal injection of carbon tetrachloride every other day for 10 weeks. The second group was chosen as an cirrhotic control and received saline, the third group was given silymarin orally (80 mg/kg/day) throughout the induction of cirrhosis and the fourth group was given silymarin orally (80 mg/kg/day) for 10 weeks after induction cirrhosis. For laboratory evaluation of functional state of liver, serum glutamic oxalacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), Alkaline phosphatase, bilirubin, free fatty acids, triglycerides and total cholesterol were estimated. In addition, histopathological study of liver was performed.

Simultaneous administration of silymarin with CCL<sub>4</sub> throughout the induction of cirrhosis (Group III) i. e. as prophylactic agent produced marked improvement in the histopathological changes of liver and completely normalized the biochemical abnormalities of CCL<sub>4</sub> induced liver cirrhosis. On the other hand, administration of silymarin for the same period after cirrhosis (Group IV) i. e. as a therapeutic agent produced partial improvement of the

histopathological changes and significant but not complete correction of the biochemical abnormalities.

The results of the present study indicate that silymarin has both prophylactic and therapeutic effects. However,

its prophylactic use exerts a more hepatoprotective effects than its therapeutic use. This point is worthy to be considered in the clinical use of silymarin as early as possible in the management of any hepatic disease or on exposure of the liver to any injurious agent.

Table (1) : Prophylactic effect of silymarin on serum biochemical changes in rats with induced liver cirrhosis.

Test	Saline 0.5ml.I.P Every Other day for 10 weeks (Group I)	CCL4 Every Other Day I. P. For 10 Weeks ( Group II )		Silymarin 80 mg/kgm/day Orally for 10 week Simultaneously with CCL4 Administration (Group III)		
	Mean $\pm$ S. E. (n = 15)	Mean $\pm$ S. E. (n = 15)	P	Mean $\pm$ S. E. (n = 15)	P	P.I
Serum glutamic pyruvic transaminase (I. U. / ml).	42.0 $\pm$ 3.48	76.0 $\pm$ 4.56	< 0.001	46.83 $\pm$ 1.51	N. S.	< 0.001
Serum glutamic oxalacetic transaminase (I. U. / ml).	60.4 $\pm$ 3.51	101.66 $\pm$ 2.81	< 0.001	59.60 $\pm$ 1.3	N. S.	< 0.001
Serum alkaline phosph. (I. U. / L.)	40.16 $\pm$ 1.8	58.16 $\pm$ 1.88	< 0.001	44.60 $\pm$ 0.42	N. S.	< 0.001
Serum Bilirubin (mg/100ml.)	0.176 $\pm$ 0.008	0.66 $\pm$ 0.04	< 0.001	0.295 $\pm$ 0.02	N. S.	< 0.001
Serum total cholesterol. (mg/100ml.)	112.3 $\pm$ 2.3	73.4 $\pm$ 1.2	< 0.001	111.7 $\pm$ 2.1	N. S.	< 0.001
Serum Triglycerides. (mg/100ml.)	93.3 $\pm$ 1.33	75.3 $\pm$ 1.4	< 0.001	89.66 $\pm$ 1.47	N. S.	< 0.05
Serum free fatty acids. (mg/100ml.)	7.66 $\pm$ 0.6	15.16 $\pm$ 0.6	< 0.001	6.6 $\pm$ 0.38	N. S.	< 0.001

S. E. = Standard error of the mean.

N. S. = P > 0.05

n = Number of animals.

P = Significance of the difference between the means of the test group and control group.

P = Significance of the difference between the means of the test group and CCL<sub>4</sub> treated group.

Phosph. = Phosphatase.

**Table (2) :** Therapeutic effect of silymarin on serum Biochemical changes in rats with induced liver cirrhosis.

Test	Saline 0.5ml.I.P Every Other day for 10 weeks (Group I)	CCL <sub>4</sub> Every Other Day I. P. For 10 Weeks (Group II)		Silymarin 80 mg/kgm/day Orally for 10 weeks after CCL <sub>4</sub> Administration (Group IV)		
	Mean $\pm$ S. E. (n = 15)	Mean $\pm$ S. E. (n = 15)	P	Mean $\pm$ S. E. (n = 15)	P	Pi
Serum glutamic pyruvic transaminase (I. U. / ml).	42.00 $\pm$ 3.48	76.0 $\pm$ 4.56	< 0.001	53.3 $\pm$ 2.32	<0.05	< 0.001
Serum glutamic oxalacetic transaminase (I. U. / ml).	60.40 $\pm$ 3.51	101.66 $\pm$ 2.81	< 0.001	82.83 $\pm$ 4.9	<0.01	< 0.01
Serum alkaline phosph. (I. U. / L.)	40.16 $\pm$ 1.8	58.16 $\pm$ 1.88	< 0.001	45.5 $\pm$ 1.66	<0.05	< 0.001
Serum Bilirubin (mg/100ml.)	0.176 $\pm$ 0.008	0.66 $\pm$ 0.04	< 0.001	0.44 $\pm$ 0.036	<0.001	< 0.001
Serum total cholesterol. (mg/100ml.)	112.3 $\pm$ 2.3	73.4 $\pm$ 1.2	< 0.001	108.3 $\pm$ 1.8	N. S.	< 0.001
Serum Triglycerides. (mg/100ml.)	93.3 $\pm$ 1.33	75.3 $\pm$ 1.4	< 0.001	98.4 $\pm$ 1.2	N. S.	< 0.001
Serum free fatty acids. (mg/100ml.)	7.66 $\pm$ 0.6	15.16 $\pm$ 0.6	< 0.001	10 $\pm$ 0.57	<0.05	< 0.001

S. E. = Standard error of the mean.

N. S. = P > 0.05

n = Number animals.

P = Significance of the difference between the means of the test group and control group I.

Pi = Significance of the difference between the means of the test group and CCL<sub>4</sub> treated group.

Phosph. = Phosphatase.

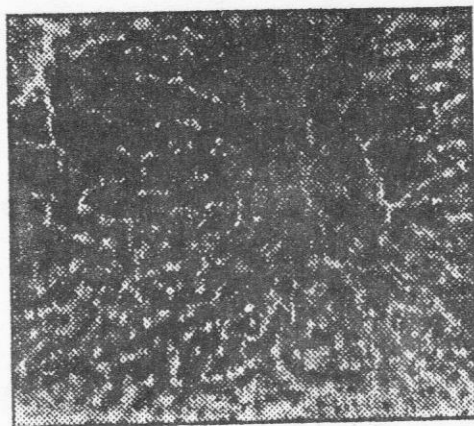


Fig. 1 : Section in liver of control rat showing normal architecture (Hx. & E. x 150).

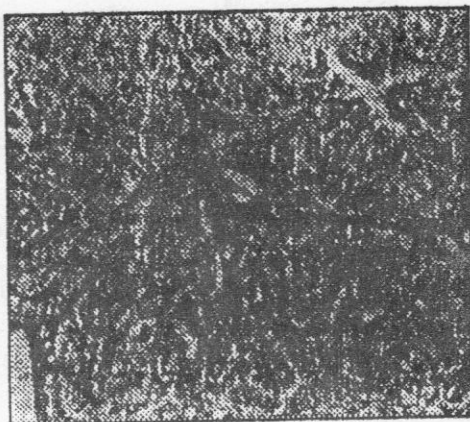


Fig. 3 : Section in liver of rat given CCL4 (cirrhotic control) showing developing cirrhosis. Curving septa extending from portal tracts between groups of liver cells (Hx. & E. x 150).

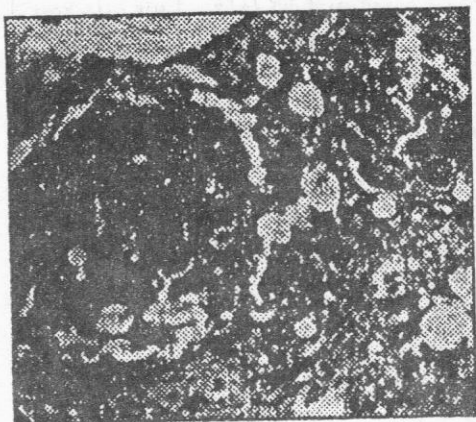


Fig. 2 : Section in liver of rat given CCL4 only (cirrhotic control) showing liver cirrhosis. The lobular architecture is lost and replaced by variable sized liver cells nodules surrounded by fibrous tissue stroma heavily infiltrated by lymphocytes. The hepatocytes showed marked hydropic degeneration with ballooning and subsequent cell death (Hx. & E. X 200).

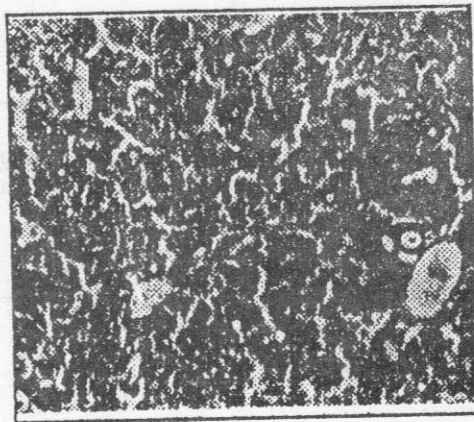


Fig. 4 : Section in liver of rat given CCL4 (cirrhotic control) showing massive necrosis involving almost all liver cells in a lobule with only a few surviving periportal hepatocytes (Hx. & E. X 150).



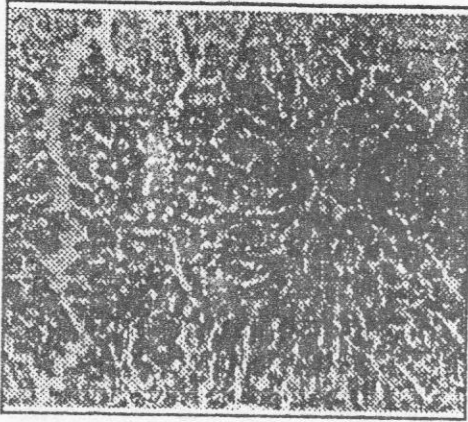


Fig. 5 : Section in liver of rat given concurrent CCL4 and silymarin showing preservation of more or less normal architecture (Hx. & E. X 150).

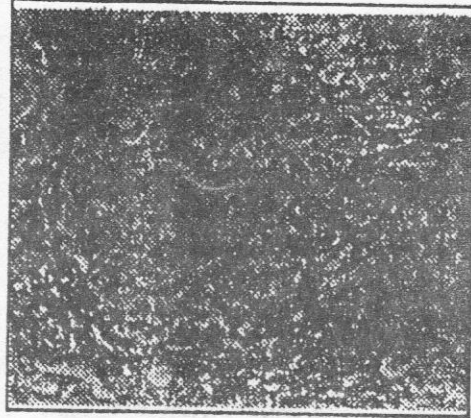


Fig. 7 : Section in liver of rat given silymarin after induction of liver cirrhosis showing slight decrease of both fibrous tissue stroma and lymphocytic infiltration (Hx. & E. X 150).

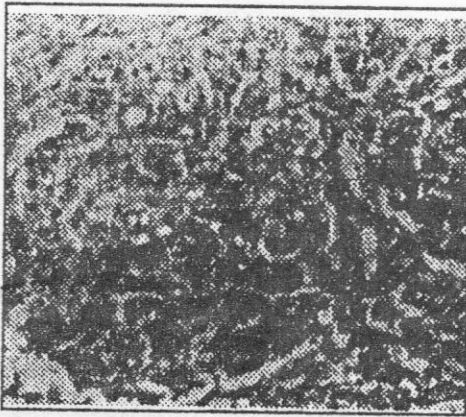


Fig. 6 : Section in liver of rat given concurrent CCL4 and silymarin and who developed cirrhosis showing marked decrease in the amount of fibrous tissue stroma around the liver cells nodules as well as lymphocytic infiltration (Hx. & E. X 150).

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## تقييم التأثير الوقائي والعلاجي لعقار السليمارين فى تليف الكبد المعملی

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### ملخص البحث:

أجرى هذا البحث لتقييم التأثير الوقائي والعلاجي لعقار السليمارين فى تليف الكبد المعملی اشتمل هذا البحث على ٦٠ فأر والتي قسمت إلى أربع مجموعات متساوية. وقد اتخذت المجموعة الأولى والغير مصابة بالتليف الكبدى كمجموعة ضابطة، أما المجموعات الثلاثة الأخرى فقد أحدث بها تليف كبدى بواسطة حقن رباع كلوريد الكربون فى الغشاء البروتونى ثلاث مرات اسبوعياً لمدة عشرة أسابيع، وقد استخدمت إحدى هذه المجموعات المصابة بتليف كبدى كمجموعة ضابطة ولقد عولجت المجموعة الثالثة بعقار السليمارين عن طريق الفم (٨٠ مجم/كجم/يومياً) وذلك خلال أحداث التليف الكبدى، أما المجموعة الرابعة فقد عولجت بعقار السليمارين عن طريق الفم (٨٠ مجم / كجم / يومياً) لمدة ١٠ أسابيع بعد أحداث التليف الكبدى. ولقد تم قياس وظائف الكبد (انزيمات)، ونسبة الصفراء، والفوسفاتيز القلوى، الأحماض الدهنية الحرة، والجلسيدات الثلاثية والكوليستيرول، وبالإضافة إلى ذلك فقد تم عمل دراسة هستوباثولوجية للكبد.

وقد وجد أن الحقن المتلازم لعقار السليمارين عند أحداث التليف الكبدى (المجموعة الثالثة) كعامل وقائي أظهر تحسن واضح فى التغيرات الهستوباثولوجية للكبد وكذلك فقد أعاد التغيرات الكيميائية التى أحدثها التليف فى الدم إلى حالتها الطبيعية. ومن جهة أخرى فقد وجد أن إعطاء السليمارين بنفس الجرعة ولكن بعد أحداث التليف (المجموعة الرابعة) كعامل علاجي أظهر تحسن جزئى فى التغيرات الهستوباثولوجية وتحسن بسيط فى التغيرات الكيميائية للدم ولقد أظهرت نتائج هذا البحث أن عقار السليمارين له تأثير وقائي وعلاجي فى حالات تليف الكبد ولكن استعماله الوقائي أكثر فاعلية بالمقارنة عند استعماله كعلاج بعد حدوث التليف وهذه النقطة جديرة بأن تأخذ فى الاعتبار فى الاستعمال الاكلينيكي لعقار السليمارين مبكراً أو عند تعرض الكبد لأى عوامل ضاره.