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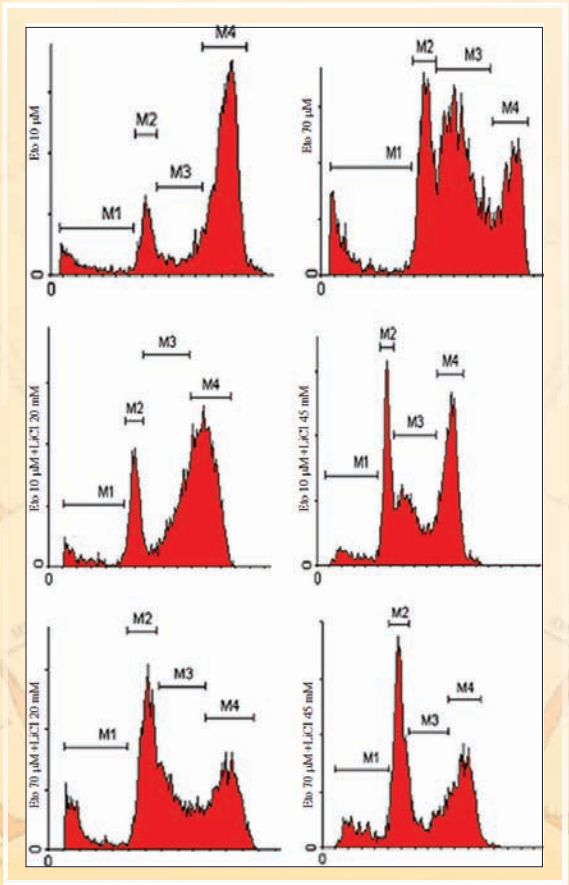

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Research Article

A study of the effect of *Nigella sativa* (Black seeds) in isoniazid (INH)-induced hepatotoxicity in rabbits

Anwar S. Hassan, Jawad H. Ahmed[1], Sawsan S. Al-Haroon[2]

Department of Pharmacy, Al-Mawanee Hospital, [1]Departments of Pharmacology, [2]Pathology and Forensic Medicine, College of Medicine, University of Basrah, Basrah, Iraq

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Correspondence to:
Prof. Jawad H. Ahmed,
E-mail: jawadahmed_basmed@yahoo.com

ABSTRACT

Objective: To investigate the possibility of hepatoprotective effect of *Nigella sativa* (NS) in INH-induced hepatotoxicity.

Materials and Methods: The experiments were carried out on 24 male rabbits. They were divided into 4 groups (6 each); rabbits in group 1 were treated with INH following a standard protocol to induce hepatotoxicity. Rabbits in group 2 received starch. Group 3 received NS 1 g/kg/day before INH treatment. Group 4 rabbits were treated with NS only. Phenobarbital sodium (IP) was given to induce metabolism of INH. INH and NS were given orally. The experiment continued for 12 days; at day 13, animals were sacrificed. Liver function tests, malondialdehyde (MDA) were estimated in serum and in liver homogenates. Liver histopathological examinations were performed.

Results: Histopathological changes of hepatotoxicity were found in all INH-treated rabbits. The histopathological findings were normal in three rabbits treated with NS before INH, very mild in two, and with moderate changes in one rabbit. Serum alanine aminotransferase (S.ALT) was elevated after INH treatment and returned back to the control value when NS was given before INH. Similar pattern of effect was noticed with serum aspartate aminotransferase (S.AST), S. total bilirubin, S. MDA, and Serum alkaline phosphatase. In liver homogenate, AST, ALT, and MDA were increased with INH treatment compared to the control, then decreased with NS treatment given before INH.

Conclusions: NS has hepatoprotective effects against INH-induced hepatotoxicity in rabbits. NS 1 g/kg proved safe, no adverse effects; no histopathological or biological abnormalities were seen.

KEY WORDS: INH, liver toxicity, *Nigella sativa*

Introduction

Isoniazid (INH) is an indispensable drug in the prophylaxis and treatment of tuberculosis, but its use is associated with serious adverse effect, such as hepatotoxicity which may result in discontinuation of treatment. Hepatotoxicity with INH in its mildest form is associated with moderate elevation in liver enzymes, it occurs in 3 to 20% of patients and the severe form of hepatotoxicity is manifested as hepatic damage, especially hepatic necrosis, which occurs in 1 to 2% of patients, if not recognized early, it may be fatal.[1,2]

The protective actions of herbs against liver damage attract interest of many researchers; *Nigella sativa* (NS) (Black cumin) is among these herbs which are found protective for the liver against drugs or chemicals.[3] Although the underlying mechanism is not well defined, the antioxidant, anti-inflammatory, and anti-angiogenesis properties of NS may play a role in this effect.[4-6] This study is aimed at investigating the possible effect of NS in protecting hepatotoxicity of INH in a rabbit model.

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Materials and Methods

Preparation of Nigella Sativa Dosage Form

NS seeds were purchased from a local market in Basrah. The seeds were identified and authenticated by an expert local pharmacist. Voucher specimens were kept in the Department of Pharmacology. The powder of NS was obtained by mechanical

grinding of the seeds. One gram was suspended in 5 ml glucose water. A dose of 1 g/kg/day was administered to each rabbit.

Preparation of Isoniazid Dosage Form

Two tablets of INH (200 mg) (MACLEODS Pharmaceutical Industries, Mumbai, India) were grinded by porcelain mortar, dissolved in 5 ml glucose water to obtain a concentration of (40 mg/ml). The powder of INH was completely dissolved to give a homogenized solution. The dose of INH corrected for body weight of rabbits was calculated.

Animal Handling

The experiments were carried out on 24 locally bred sexually mature domestic male rabbits. Their body weights ranged from 1 to 1.8 kg. The animals were housed in the main animal house of the college of medicine. They were kept in a stainless steel cage for acclimatization with a 12:12-hour light/dark cycle and free access to food and drinking water. They were not fed for 12 hours before the experiment.

Study Design

The study protocol was approved by the Institutional Ethics Committee. The study was carried out between November 2010 and September 2011.

The rabbits were randomly divided into four groups of six animals each. Group 1 (INH-treated group); the animals received starch (1 g/kg/day) daily for 12 days. INH was given at the last 2 days of the experiment in a starting loading dose of 50 mg/kg orally, then 35 mg/kg every 3 hours for three doses. Rabbits in group 2 (control group) followed the same timing steps of group 1 except substituting INH by glucose water at day 11-12 of the experiment. In rabbits in group 3 (NS + INH), the same protocol as in group 1 was followed, but starch was substituted by NS. In group 4 (NS), the rabbits received suspension of NS (as in group 3), INH was omitted and substituted by glucose water. On day 8 and for the following 3 days, according to Sarich *et al.*'s protocol,[7] phenobarbital sodium 25 mg/kg/day (Alex Pharmaceutical Industries, Alexandria, Egypt) was administered to all animals by i.p. route.

Blood Sampling and Tissue Handling

On the morning of day 13, 5 ml of blood were taken directly from the heart under light ether anesthesia; blood was centrifuged to isolate the serum for liver function test and malondialdehyde (MDA) measurements. The rabbits were then sacrificed; liver specimens were obtained for the biological measurements and for histopathological examination.

Histopathological Examination

The specimens were examined by a specialist histopathologist (A.S.S) at the Department of Pathology and Forensic Medicine, Basrah College of Medicine. The examiner was blinded for the treatments.

Preparation of Liver Homogenate

Liver tissues were homogenized in cold phosphate buffer saline (pH = 7.4) to obtain 10% of liver homogenate (using Hiedolph electrical homogenizer, Korea) at 6 000 rpm for 20 minutes.

Laboratory Measurements

Estimation of serum malondialdehyde

Thiobarbituric acid assay of Beuge and Aust (1978)[8] was used for measuring serum MDA.

Estimation of liver malondialdehyde

MDA levels in liver homogenates were estimated as described by Ohkawa *et al.*, 1979.[9]

Liver function tests

The activities of serum aspartate aminotransferase (S.AST) and serum alanine aminotransferase (S.ALT) were estimated using commercially available kits (Randox diagnostic reagents, Randox Laboratories, USA). Serum alkaline phosphatase (S.ALP) and serum total bilirubin were estimated by commercially available kits (Biolabo reagents, Biolabo SA, France).

Statistical Analysis

SPSS computer package version 15 was used for statistical analysis. Data were analyzed by one-way ANOVA. Tukey HSD (Honestly Significant Difference) test was used to compare between the means. The differences were considered significant at $P<0.05$. The results were expressed as mean ± SD, unless otherwise stated.

Results

Histopathological Examination

The control group

There were no histopathological changes in all liver samples obtained from rabbits in this group ($n = 6$). A representative histopathological slide is presented in Figure 1a.

Nigella sativa group

As in the control group, treatment with NS revealed no histopathological changes in the liver [Figure 1b].

INH group

There were considerable histopathological changes in all animals in this group ranging from moderate to severe hepatotoxicity. These changes were characterized by:

1. Inflammation of portal globular and perivenular inflammatory cell infiltration, mainly neutrophils
2. Sinusoidal dilatation (mainly lobular)
3. Hepatocellular necrosis
4. Moderate portal inflammation, degeneration of hepatocytes, fatty changes around central vein, marked fatty vacuolization
5. Moderate lymphocytic infiltration with extension of inflammation and bridging with other portal tract
6. Moderate portal lymphocytic infiltration, ballooning degeneration around central vein [Figure 1c].

Nigella sativa + INH group

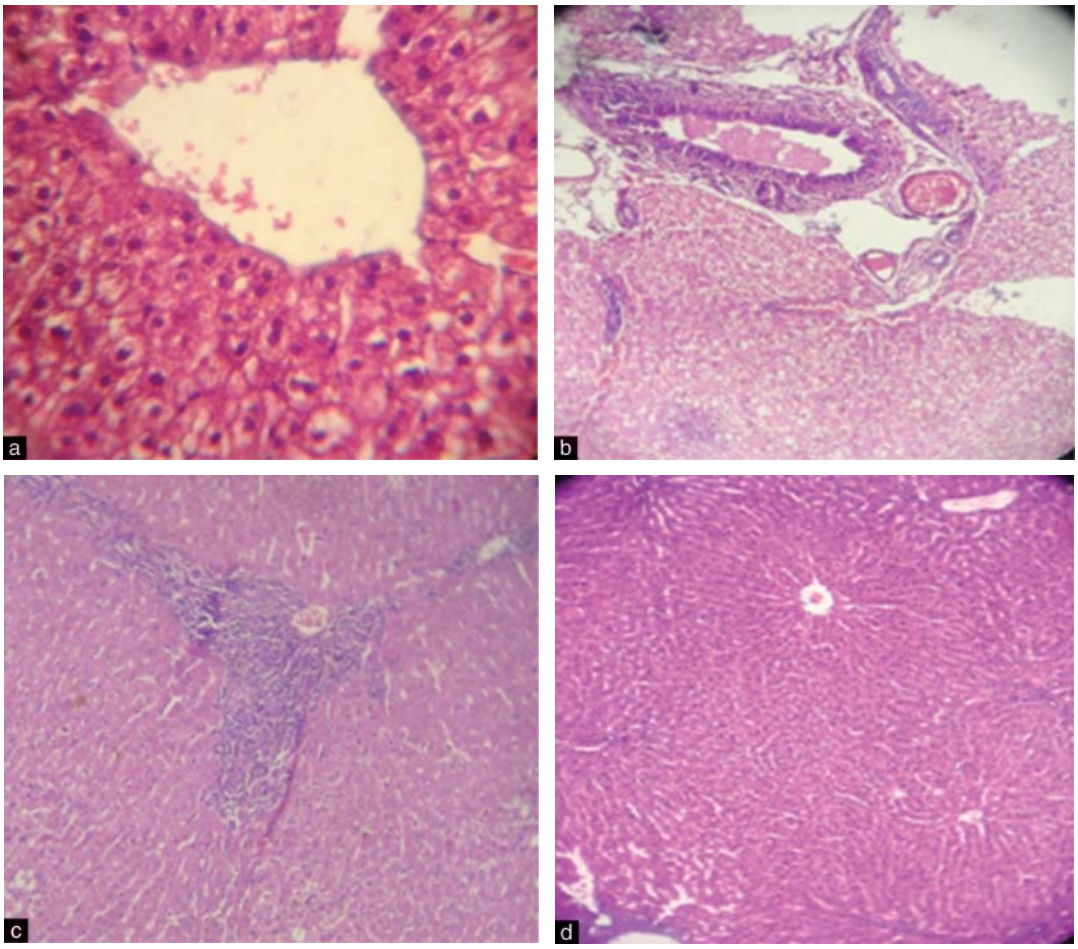
The livers appeared completely normal in three rabbits, two with mild inflammation and in one rabbit moderate inflammatory changes were observed. In the rabbits with mild histopathological changes, there was a mild portal tract inflammation, while in the rabbit with moderate changes, inflammation, perivenular degeneration of hepatocytes was seen [Figure 1d].

The Effect of Treatments on Serum Liver Enzymes

The effect on aspartate aminotransferase in the serum

The mean S.AST level of the control group was 14 ± 5.1 IU/l; this was not significantly different from 14.5 ± 4.1 IU/l in NS-treated group. Treatment with INH has resulted in a significant rise in S.AST level to 36.2 ± 16.1 IU/l in comparison to the control group ($P<0.01$) [Table 1]. Treatment with NS before INH

Figure 1: (a) A healthy liver tissue from a rabbit on starch and phenobarbital sodium (group 2). The central vein appears in the middle of the field. (Hematoxylin-Eosin stain, 400X). (b) A liver tissue from a rabbit receiving *Nigella sativa* and phenobarbital sodium. Portal area, bile duct, and hepatic vein are shown. The field appears clear with no sign of inflammatory cell infiltration (Hematoxylin-Eosin stain, 200X). (c) A liver tissue from a rabbit on starch and phenobarbital sodium then treated with INH (group 1). Hepatic vein is shown in the middle of the field. Moderate lymphocytic infiltration with extension of inflammation and bridging with other portal tracts (Hematoxylin-Eosin stain, 100X). (d) A liver tissue from a rabbit receiving *Nigella sativa* before phenobarbital sodium and INH treatment (group 3). The central vein and the surrounding area of the liver tissue appear normal (Hematoxylin-Eosin stain, 100X)



significantly reduced S.AST level from 36.2 ± 16.1 IU/l in the INH-treated group to 13.2 ± 5.6 IU/l ($P<0.01$) in the rabbits pretreated with NS.

The effect on alanine aminotransferase in the serum

The serum levels of ALT of the control group and the NS-treated group were 10.3 ± 3.4 IU/l and 12 ± 4.4 IU/l, respectively, which were not significantly different. There was an increase in the level of ALT to 25 ± 12.2 IU/l in the INH-treated group. This rise in ALT is significantly different from that of the control ($P<0.05$). The level of ALT was significantly lower in the rabbits treated with NS before INH in comparison to the INH values (10.7 ± 4.5 *vs* 25 ± 12.2 IU/l); the difference was statistically significant ($P<0.05$) [Table 1].

The effect on serum alkaline phosphatase

There was an increase in S.ALP in the INH-treated rabbits compared to the control. The respective values of the control group, NS, INH, and the combination INH and NS were 75.3 ± 19.6, 77.3 ± 19.2, 102 ± 20.5, and 80.3 ± 18.8 IU/l. There were no statistical differences between them [Table 1].

The effect on serum total bilirubin

The serum total bilirubin was (0.42 ± 0.32 mg/dl) in the control group. This level was lower in the NS-treated rabbits (0.2 ± 0.06 mg/dl) but it did not achieve statistical significance. INH treatment significantly increased total serum bilirubin to 0.98 ± 0.6 mg/dl compared to the control and NS groups [Table 1]. Treating the rabbits with NS before INH significantly lowered the total serum bilirubin to 0.25 ± 0.19 mg/dl in comparison to INH alone ($P<0.05$).

The Effect of Treatments on the Liver Enzymes in Liver Homogenates

The effect on aspartate aminotransferase in liver homogenates

The mean value of AST in liver homogenates in the control group was 60 ± 7.1 IU/g. This level was 41.5 ± 19.6 IU/g in the NS-treated rabbits, which was not significantly different from control. Treatment with INH significantly increased AST in liver homogenate to 84.8 ± 12.1 IU/g in comparison to the control or NS-treated group ($P<0.05$).

Treatment with NS before INH significantly decreased AST level in liver homogenate to 54 ± 16 IU/g in comparison to the INH value ($P<0.01$) [Table 2].

The effect on alanine aminotransferase in liver homogenates

The mean value of ALT in the liver homogenate of the control group was 62 ± 16.6 IU/l [Table 2] which was not significantly different from 65.5 ± 12 IU/l in the NS-treated group. There was a small and insignificant increase in ALT in the rabbits treated with INH (75 ± 6.7 IU/l) compared to the control or the NS-treated values. However, there was marginally significant reduction ($P = 0.053$) in the level of ALT (54.5 ± 15.2 IU/l) in liver homogenate in the rabbits treated with NS prior to INH treatment in comparison to INH alone.

The Effect of Treatments on Malondialdehyde Level

The effect on malondialdehyde level in the liver homogenate

The mean control value of MDA in liver homogenate was 406 ± 260 ηmol/g, which was lower but statistically not significantly different from 293 ± 77.9 ηmol/g in NS.

MDA was significantly increased from 406 ± 260 in the control group to 946.3 ± 338.3 ηmol/g in the INH-treated rabbits ($P<0.01$). Treatment with NS prior to INH administration significantly reduced MDA level to 448.5 ± 177 ηmol/g in comparison to INH alone ($P<0.05$) [Table 3].

The effect on serum malondialdehyde level

The mean serum MDA of the control was 0.35 ± 0.26 μmol/l. This was statistically not different from 0.32 ± 0.16 μmol/l in the NS-treated rabbits. INH treatment increased serum MDA level to 0.938 ± 0.37 μmol/l, which was significantly higher than the control or NS values ($P<0.05$). Treatment with NS before INH decreased serum MDA to 0.373 ± 0.053 μmol/l. which was significantly lower than that of INH treatment ($P<0.01$) [Table 3].

Discussion

Not many animal models that resemble INH-induced hepatotoxicity in human are available; however, Sarich *et al.* (1995)[7] found the rabbits as a good and sensitive model for INH-induced hepatotoxicity. Phenobarbital sodium, an enzyme inducer, induces hepatotoxicity in more than 90% of the animals receiving INH when given before INH. Phenobarbital is not known to have hepatotoxicity and hepatoprotective effects. Practically, pretreatment with phenobarbital before INH produces hepatotoxicity in almost all animals irrespective to their acetylation status (the rabbits as human can be grouped as fast or slow acetylators for INH).[10]

Treatments were given orally since oral route is the usual way of prescribing INH to human beings. INH, through this route, goes directly to the liver via the portal vein with a great exposure of the liver to INH. Once INH reaches the liver, it is metabolized to a hepatotoxic metabolite hydrazine.[7]

Since INH and NS were given orally, a gap of 1.5 to 2 hours separated the administration of the two to avoid possible interaction in the GIT.

Table 1:

The effect of pretreatment with *Nigella sativa* on INH-induced changes in serum liver enzymes in rabbits (Mean ± SD)

Laboratory measurements	Control group	Nigella sativa-treated group	INH-treated group	Nigella sativa + INH-treated group
S. ALT IU/l	10.3±3.4	12±4.4	25±12.2[a]	10.7±4.5
S. AST IU/l	14±5.1	14.5±4.1	36.2±16.1[b]	13.2±5.6
S. ALP IU/l	75.3±19.6	77.3±19.2	102.2±20.5	80.3±18.8
S. Total bilirubin mg/dl	0.42±0.32	0.2±0.06	0.98±0.6[c,d,e]	0.25±0.19

[a]$P<0.05$, [b]$P<0.01$: Significantly different from the corresponding values of the control, *Nigella sativa*, and the combination *Nigella sativa* + INH groups, [c]$P<0.01$: Significantly different from *Nigella sativa* treatment, [d]$P = 0.057$: Marginally significant difference from the control, [e]$P<0.05$: Significantly different from the combination *Nigella sativa* + INH

Table 2:

The effect of pretreatment with *Nigella sativa* on INH-induced changes in liver enzymes of the liver homogenate in rabbits (Mean ± SD)

Laboratory measurements	Control group	Nigella sativa-treated group	INH-treated group	Nigella sativa + INH-treated group
Liver AST	60±7.1	41.5±19.6	84.8±12.1[a,b,c]	54±16
Liver ALT	62±16.5	65.5±12	75.5±6.7	54.5±15.2[d]

[a]Significantly different from the corresponding value of the *Nigella sativa* treatment, $P<0.05$, [b]Significantly different from the corresponding value of the control, $P<0.05$, [c]Significantly different from the corresponding value of the combination *Nigella sativa* + INH, $P<0.01$, [d]Marginal difference from the corresponding value of the INH treatment, $P = 0.053$

Table 3:

The effect of pretreatment with *Nigella sativa* on INH-induced changes in malondialdehyde (MDA) level in the serum and liver homogenate in rabbits (Mean ± SD)

Laboratory measurements	Control group	Nigella sativa-treated group	INH-treated group	Nigella sativa + INH-treated group
Serum MDA (μmol/l)	0.35±0.26	0.32±0.16	0.938±0.37[a]	0.373±0.053
Liver MDA (ηmol/g)	406±260	293±77.9	946.3±388.3[b,c]	448.5±177

[a]Significantly different from the value of the control, Nigella sativa treated group and the combination Nigella sativa and INH, $P<0.01$, [b]Significantly different from the value of the control group and Nigella sativa treatment, $P<0.01$, [c]Significantly different from the value of the combination Nigella sativa and INH, $P<0.05$

Three of the six rabbits treated with INH had slow movement, immobility, and reduced food intake. These are probably features of INH neurotoxicity. Administration of vitamin B6 in these animals was not attempted, since B6 is reported to prevent INH-induced hepatotoxicity.[11]

All INH-treated rabbits had histopathological changes, the occurrence of which make comparison with other groups possible; thus, disappearance of histopathological changes by NS treatment can be interpreted as a true effect. The histopathological features of INH hepatotoxicity are characterized by focal and centrilobular inflammatory infiltration and necrosis, extension of inflammation and bridging, fatty vacuolization and ballooning degeneration also appears. Most of these changes can be seen in INH-induced hepatotoxicity in human beings, which are hardly distinguishable from histopathological features found in viral hepatitis.[12,13] It is worth mentioning that there were no histopathological changes in the rabbits solely treated with NS. The histopathological features in this group are not different from that in the control group. These findings support previous reports that NS is not harmful to the liver.[6,14]

Moreover, the results of the present study confirmed the usefulness of NS in folk medicine as liver saver,[4] and also support many studies which showed NS oil extract or the aqueous suspension of the seeds as hepatoprotective against many hepatotoxins.[6,14-16] None of these reports had studied NS in INH-induced hepatotoxicity. Although the mechanisms behind the hepatoprotective effects of NS are not well known, there are many possible mechanisms; NS has antioxidant properties.[15,17] In the present study, there was a significantly higher level of MDA, a marker of oxidative stress, in the serum and in liver homogenate in INH-treated rabbits, which is markedly declined when NS treatment is administered before INH. In addition, hepatoprotection, *in vitro* as well as *in vivo* in which antioxidant potentials of NS was suggested, was reported with thymoquinone and other active constituents of NS.[4,18]

Pretreatment with NS in INH-treated rabbits decreased elevated liver enzymes. These findings support the previously reported findings that NS seeds restored the enzymes level in carbon tetrachloride (CCl4)-induced hepatotoxicity in rats.[15] In another study, pretreatment with thymol, an active constituent of NS, prevents any increase in liver enzymes in rodents in which hepatotoxicity was induced by CCl4 or paracetamol.[19]

Another possible mechanism for the hepatoprotective effect of NS is its role in inflammation. Inflammatory changes play an important role in drug-induced acute hepatitis and products of arachidonic acid are extensively involved in the inflammatory process.[20] On the other hand, it was found that the hepatotoxic metabolite of INH, hydrazine, participates in a significant production of H2O2, a cellular mediator of inflammation, which has a major role in the manifestation of adverse drug reactions.[21] Thymol and thymoquinone was found to have anti-inflammatory effects;[22,23] thus, a hepatoprotective effect of NS due to an anti-inflammatory effect cannot be ruled out.

It can be concluded that NS powder given orally has a hepatoprotective effect against INH-induced hepatotoxicity in rabbits.

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