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Human Diseases Prosecution Among Viral Infection and Food Toxins: A Review

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Abstract: Hepatitis B and C viruses are major etiologic agents of acute and chronic viral hepatitis especially in many developing countries by which the food toxins sustained viral hepatocarcinoma. Developed abnormal liver lesions were found in mice during infection with hepatitis B virus×protein and exposure to diethylnitrosamine. In addition, chronic HBV infection and exposure to dietary aflatoxin are important risk factor in the development of hepatocellular carcinoma. Whereas lymphocyte infiltration to periportal areas and damaged bile duct are usually recognized in liver with chronic hepatitis C virus. Moreover, biogenic amines, i.e., histamine, cadaverine or putrescine were found to cause hepatocytes inflammation and lesions during intraperitoneally injection of mice. Moreover, hepatocytes apoptosis was a human pathological feature as a result of alcoholic consumption.

Key words: Hepatitis C, hepatitis B, biogenic amines, alcoholic hepatitis

INTRODUCTION

In the United States, 2000 cases of Acute Liver Failure (ALF) as viral infection have been reported each year (Lee, l993). Moreover, Suzuki *et al*. (1998) found that the prevalence of occult hepatitis B infection in patients with non A, non B, ALF vary from a low value of 0 to 4% in Europe, meanwhile, to 50% in Japan. Although, an effective vaccine exists, HBV infection is still a serious public health problem; more than 240 million people are chronically infected with HBV worldwide and about 25% of them die of chronic active hepatitis, cirrhosis or hepatocellular carcinoma (Lai and Yuen, 2008; Liaw and Chu, 2009). Similarly, Hepatitis C Virus (HCV) infection is a major public health problem (Lavanchy, 1999), in which there are approximately 130-200 million people infected with the Hepatitis C Virus (HCV) worldwide (Gravitz, 2011; Chak *et al*., 2011). Despite, many investigators described interferon α and β for inhibition of viremia proliferation.

Diagnosis of HCV based on serological detection of anti-HCV antibodies by Enzyme Linked Immune Sorbent Assay (ELISA), supplemented with Recombinant Immunoblot Assay (RIBA). The detection of HBV in serum of some patients with ALF despite testing negative for hepatitis B surface antigen (Anti HBVIgm), had detected the DNA of HBV in serum by Polymerase Chain Reaction (Teo *et al*., 2001). In general, hepatitis B virus surface antigen (HBsAg) is the most crucial serum marker in the fast screening and clinical diagnosis of HBV infection (Dienstag, 2008; Gu *et al*., 2009; Liu *et al*., 2014). The role of food toxins in sustaining of viral infection has been reported by Slagle *et al*. (1996), in which they found that single dose of 2 μg g^{-1} b.wt. of diethylnitrosamine (DEN) enhanced hepatocarcinoma in mice carrying the hepatitis B virus×gene.

Moreover, the injection of 100 μmole of histamine, cadaverine or putrescine causing hepatocyte inflammation and lymphocyte infiltration around the central vein of liver of mice (El-Hersh, 2002). On the other hand, Alcoholic Hepatitis (AH) is a toxic liver disease, since tunnel and caspase-3-positive hepatocytes were readily observed in the liver of patients consumed high amount of alcoholic beverages and apoptosis cases were also recorded as reported by Natori *et al*. (2001).

DIAGNOSIS OF HBV AND/OR HCV INFECTION

Acute HBV infection has been reported in 50 to 60% of patients with ALF in small case series in United States. Teo *et al*. (2001) pointed out that HBV-DNA was detected in the sera of 9 individual, the equal to 6% of the tested patients with ALF by HBV genotypes A, B, C and D as shown in Table 1. Moreover, 7 of these nine patients has

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Table 1: HBV genotypes, precore and core promoter changes in patients with fulminant hepatitis B

						Core promoter		
Patient No.	Race	Sex	Age	HBeAG	HBV genotype	Nt_{1762}	Nt_{1762}	Precore Nt_{1896}
1	White	M	54	Neg	D	A	G	A
2	White	M	63	Neg	C	A	G	A
3	Black	M	50	Pos	A	A	G	G
4	White	F	17	Neg	D	A	G	$G_{1817}T$
5	Black	F	43	Pos	A	T	A	G
6	Asian	F	62	Neg	B	A	G	A
7	White	M	58	Pos	A	A	G	G
8	White	M	62	Neg	D	T	A	A
9	White	F	30	Neg	A	A	A	$G_{1897}A$

Teo *et al.* (2001)

Table 2: Demographic, clinical and virological serum PCR positive and negative patients

Variables	PCR positive (n = 100)	PCR-negative (n = 33)	Statistical analysis
Mean age at diagnosis (SD)	43.6 (SD) 7.4)	43.1±7.5	NS
Source/duration of infection (%)			
No. received HCV infected anti-D in 1977	86(86%)	28(85%)	NS
No. received HCV infected anti-D between 1991-1993	14(14%)	5 (15%)	
Genotype 1	86	NT	
Genotype 3	14	NT	
RIBA status (%)	100	29 (87.9%)	
Positive			
Indeterminate	0	4 (12.1%)	p<0. 001
Mean ALT (IU L^{-1}) (SD)	58.73 (SD 40)	27.4±18	p<0.001
Alcohol >14 (%)	6 (6%)	1 (3%)	NS
Steatosis (%)	9(10.3%) n = 87	13 (39.4%)	p<0.001
Mean HAI±SD	4.2 (SD 1.4)	1.9±1.51	p<0.001
Mean fibrosis±SD	1.) (SD 1.3)	0.15±0.4	p<0.00

NT, Serum PCR-negative individuals could not be genotyped, *Steatosis refers to the absolute No. of patients with any steatosis in the PCR-positive and negative groups after Barrett *et al.* (2001)

precore and/or, core promoter variants. In addition, data revealed that precore region has mutations in 6 patients, 4 of them had the commonly described stop-codon mutation, eW28x/G1869 A (TGG to TAG). One patient also had aprecore stop-codon mutation at position-28, but the G-to-A change involved nucleotide 1897, ew28x/G 1896 A (TGC to TGA). The remaining patient had aprecore start-codon mutation, G 1817T (ATG to ATT). All 6 patients were hepatitis B antigen (HBeAg)-negative. All patients except the one with the ew28x/G1897 A (TGG to TGA) mutation infected with non-A HBV genotypes. Overall 7 of the 9 individuals (78%) patient with fulminant hepatitis B had mutations in the precore or core promoter region. Moreover, HBV precore stop codon variants had been detected in 88-100% of patients with ALF in Japan (Omata *et al.*, 1991), 83% in Israel (Liang *et al.*, 1991) and 36% in Taiwan (Hsu *et al.*, 1995), 10% in France and 5% in the US (Teo *et al.*, 2001). These results confirmed the accuracy of HBV DNA detection by PCR in diagnosis of HBV infection, by which the findings of Fukai *et al.* (1998) showed that some patients with ALF despite testing negative for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody immunology M (anti-HBC IGM) had detected Hepatitis B Virus (HBV) DNA in the serum or liver using polymerase chain reaction. Currently, hepatitis B virus surface antigen (HbsAg) is the most crucial serum marker in the fast screening and clinical diagnosis of HBV infection (Dienstag, 2008), particularly in the western pacific area (China, South Korea and Taiwan) where the HBsAg serum prevalence ranges between 10 and 12% (Custer *et al.*, 2004). Generally, methods for detecting the serum HBsAg mainly are chemiluminescence methods, ELISA and Golden Immunochromatographic Assay (GICA) (Gu *et al.*, 2009; Liu *et al.*, 2014). However, immunoassay methods for detection of Hepatitis C Virus (HCV), i.e., RIBA and/or ELISA were not sufficient to diagnose HCV infection, since the studies of Barrett *et al.* (2001) showed that all PCR-positive HCV patients were RIBA positive, whereas, 29 (87.9%) serum PCR-negative patients were RIBA positive and 4 (12.4%) were RIBA indetermined (Table 2 and 3). In addition, histological studies of HCV PCR-negative serum of patients as revealed in Table 4 showed that Necroinflammation and Fibrosis were mild in the majority of HCV PCR-positive patient biopsied. Thirty nine (39%) had minimal inflammatory activity, 60(60%) had mild inflammation and 1(1%) had moderate liver diseases as found by Barrett *et al.* (2001) and these findings supported 'the previous detection methods. Lichtinghagen *et al.* (2001) studied the chronic HCV by which metalloproteinase and its inhibition was assessed

Table 3: Clinical data of serum PCR-negative individuals

Patients	RIBA status	C100	C33	C22	N55	BMI (kg m^{-2})	A (IU L^{-1})	Indications for biopsy	Alcohol (U week^{-1})
1	Positive	0	2	4	0	27.20	21	Patient request	3
2	Positive	0	1	0	1	22.70	21	RIBA-positive+symptoms	1
3	Positive	2	3	4	0	25.00	14	RIBA-positive+symptoms	4
4	Indeterminate	0	0	3	0	17.50	31	Symptoms	2
5	Positive	1	1	4	0	25.80	27	Patient request	1
6	Positive	1	4	0	0	26.80	14	RIBA-positive+symptoms	N/A
7	Indeterminate	0	0	0	1	24.00	16	Patient request	6
8	Positive	2	1	0	0	22.60	22	RIBA-positive+symptoms	3
9	Positive	4	2	0	0	27.70	19	RIBA-positive	N/A
10	Positive	0	1	2	0	25.70	20	RIBA-positive+symptoms	1
11	Positive	2	1	4	0	21.10	19	RIBA-positive	8
12	Positive	1	1	3	0	20.90	24	RIBA-positive	42
13	Positive	0	1	2	0	26.60	14	RIBA-positive+symptoms	5
14	Indeterminate	0	2	2	0	23.20	25	RIBA-positive+symptoms	N/A
15	Positive	0	2	0	0	27.80	46	Elevated ALTs	5
16	Positive	3	4	4	0	32.20	26	RIBA-positive+symptoms	1
17	Positive	0	2	1	0	40.60	108	Elevated ALTs+symptoms	N/A
18	Positive	0	3	4	2	16.30	13	RIBA-positive+symptoms	2
19	Positive	1	2	4	2	29.10	18	RIBA-positive+symptoms	1
20	Positive	2	1	4	0	22.70	23	RIBA-positive+symptoms	1
21	Positive	4	2	0	0	23.60	28	RIBA-positive+symptoms	3
22	Positive	0	1	4	0	23.01	18	Patient request	12
23	Positive	0	1	3	0	20.03	25	Patient request	1
24	Positive	1	0	2	0	27.80	44	Elevated ALTs+symptoms	N/A
25	Positive	2	4	4	4	32.00	11	RIBA-positive	N/A
26	Positive	2	4	4	0	26.90	20	RIBA-positive+symptoms	2
27	Positive	4	4	4	4	29.30	21	RIBA-positive+symptoms	4
28	Positive	1	2	0	0	33.50	65	Elevated ALTs+symptoms	N/A
29	Positive	4	2	0	0	23.40	23	RIBA-positive+symptoms	3
30	Indeterminate	0	0	1	0	32.40	43	Elevated ALTs+symptoms	N/A
31	Positive	3	4	4	4	18.80	23	RIBA-positive+symptoms	N/A
32	Positive	0	4	4	0	27.00	29	Patient request	2
33	Positive	3	3	2	0	27.80	22	RIBA-positive	3

N/A: Non applicable as these women have never consumed alcohol after Barrett *et al.* (2001)

Table 4: Histological data of serum PCR negative patients

Patient	Tested for HCV RNA*	Periportal	Lobular	Portal	HAI	Fibrosis	Steatosis	Other**
1	Yes	0	0	0	0	0	0	0
2	Yes	0	1	1	2	0	0	0
3	No	1	1	0	2	0	1	0
4	Yes	2	2	2	0	1	0	Granuloma
5	Yes	0	1	1	2	0	0	0
6	Yes	1	1	1	3	0	0	0
7	Yes	0	1	0	1	0	0	0
8	Yes	0	1	1	2	0	0	0
9	Yes	1	1	1	3	0	1	0
10	Yes	0	0	0	0	0	0	0
11	Yes	0	0	0	0	0	0	Granuloma
12	Yes	1	1	0	2	0	1	0
13	Yes	1	1	0	2	0	0	0
14	Yes	0	1	1	2	0	0	0
15	Yes	0	0	0	0	0	0	0
16	Yes	1	1	0	2	1	1	0
17	Yes	0	1	1	2	0	3	SH
18	Yes	2	2	1	3	0	1	SH
19	Yes	0	1	1	2	0	0	0
20	Yes	0	1	0	1	0	1	0
21	No	0	1	0	1	0	0	0
22	Yes	1	0	1	2	0	1	0
23	Yes	0	0	0	0	1	0	Granuloma and 3+Iron
24	Yes	1	2	2	5	0	2	SH
25	Yes	0	0	1	1	1	1	0
26	Yes	1	1	1	3	0	1	0
27	Yes	1	1	1	3	1	3	0
28	Yes	0	1	1	2	0	0	0
29	Yes	0	0	0	0	0	0	0
30	Yes	0	1	1	2	0	2	SH
31	Yes	0	1	1	2	0	0	0
32	Yes	1	1	1	1	0	0	0
33	Yes	0	1	0	1	0	0	0

*Tested for HCV RNA in liver biopsy tissue, **Steatosis was graded as none 0, mild = 1 (up to 5% of biopsy), moderate = 2 (up to 50% of the biopsy) and severe = 3 (more than 50% of the biopsy), SH: Steatohepatitis was only reported where neutrophils were present after Barrett *et al.* (2001)

Table 5: Behavior of serum ALT, HBsAg, HBeAG and HBV-DNA values under lamivudine treatment compared to pretreatment levels (week 24)

	Patients						Patients					
Weeks	1	2	3	4	5	6	1	2	3	4	5	6
ALT (IU mL^{-1})							**HBV-DNA (pg mL^{-1})**					
Pre	161	61	220	130	598	126	1070	5900	7388	1814	2980	44
25	142	48	135	94	241	108	65	5800	1735	447	121	<1
26	137	42	114	72	350	100	27	413	297	114	8	<1
28	114	56	123	126	226	65	6	270	158	45	<1	<1
32	53	47	111	177	52	48	1	134	83	1	<1	<1
36	40	59	88	99	34	58	1	125	25	<1	<1	<1
40	36	37	112	71	29	39	1	53	57	<1	<1	<1
44	33	35	114	54	30	42	1	92	34	<1	<1	<1
HBeAG (ng mL^{-1})							**HBsAG (µg mL^{-1})**					
Pre	470	7000	4100	1920	96	8	48	110	150	28	14	0.4
25	760	7000	3600	2300	164	3.9	6.1	120	92	35	14	0.3
26	530	5300	1750	1900	224	0.1	5.3	110	91	24	12	0.2
28	360	5600	4200	1620	199	NEG	5.0	105	91	20	13	0.5
32	200	4200	2750	1180	31	NEG	5.6	90	64	15	7	0.7
36	140	4600	1500	930	40	NEG	5.6	85	38	10	7	0.7
40	120	3500	1100	370	5	NEG	7.9	67	24	5	7	0.8
44	50	2400	1050	94	4	NEG	5	61	26	9.4	8	0.9

After Boni *et al.* (2001)

Table 6: Area under curve (AUC) of anti-HBs during the first month after the first vaccination Bio-Hep-B^{TM} vs. Engerix-B

Bio-Hep-B^{TM}		Engerix-B	
Vaccine No.	AUC[b]	Vaccine No.	AUC[b]
1	0.0	3	10.5
6	3251.5	4	0.0
11	367.5	5	17.5
12	448.0	7	182.0
14	105.0	8	0.0
15	511.0	9	87.5
16	126.0	10	178.5
18	0.0	13	829.5
21	336.0	17	17.5
23	70.0	20	0.0
24	280.0	22	0.0
26	0.0	25	0.0
29	140.0	27	0.0
30	17.5	28	7.0
33	276.5	31	0.0
35	357.0	32	11.2
36	7.0	34	10:5
37	644.0		
38	0.0		
Mean±SE	365.11±166	Mean±SE	85.44±48

[a]p = 0.0121 (Wilcoxon non-paired test), [b]Expressed in mL U mL^{-1}×day, after Shapira *et al.* (2001)

as the marker of fibro proliferation. Another study, showed the role of HCV in bile duct damage and this feature may be a characteristic of chronic HCV, in which the bile duct damage may be a result of the host's immuno reaction against HCV-infected bile duct cells (Haruna *et al.*, 2001).

HEPATITIS VIRUSES MANAGEMENT

HBV management: Hepatitis B Virus (HBV) Cytotoxic T Lymphocyte (CTL) response in patients with chronic HBV infection is generally weak or totally undetectable and the CTL hyporesponsitivity is a crucial determinant of viral persistence. However, amplification of CTL response *in vivo* may be ineffective if HBV-specific CD8 cells are either absent or non-responsive to exogenous stimulation. Correction of CTL hyporeactivity is likely to be a crucial step in the treatment of chronic hepatitis B virus (Chisari and Ferrari, 1995). It has been found that during the course of lamivudine (3TC) treatment of chronic HBV as shown in Table 5, can restore CTL reactivity making CTL susceptible to exogenous stimulation and this effect may enhance the probability that T cell-based immune therapies delivered after lamivudine treatment can successfully reconstitute a protective CTL response able to cure chronic HBV infection (Boni *et al.*, 2001). In contrast, prolonged lamivudine (3TC) therapy is associated with the occurrence of viral resistance in 15-30% after one year of treatment (Dienstag *et al.*, 1999) and these resistant elucidated genetically in which viral genome harboring mutations in the YMDD motif within the C domain of the Hepatitis B Virus (HBV) reverse transcriptase, as well as in the B domain (Seigneres *et al.*, 2001). Moreover, there are contradictory reports on the replication level of lamivudine (3TC) resistant mutants in the duck HBV (DHBV) model and the clinical severity of the liver disease associated with drug resistance. Desferrioxamine, iron depleted agent has been found to affect on the HBV life cycle indirectly through the cell cycle arrest and directly through the inhibition of viral DNA secretion as reported by Chouteau *et al.* (2001).

Immunization of hepatitis B infected patients with pre-s I /pre-s2/s (bio-Hep-B) versus a yeast derived S vaccine (Engerix-B) has been reported by Shapira *et al.* (2001). Following primary immunization (Table 6) seroprotection has been occurred in 39, 53 and 60% in the bio-Hep-B group at weeks 1, 2, 3 and 4 compared with 0, 12, 18 and 12.5% in the engerix-B vaccines, respectively. Moreover, six months following injection of the 1st dose,

seroprotection was 70 and 25% in pre-s/s and S vaccines, respectively. Commonly, bio-hep-B induces rapid seroprotection against HBV in 60-70% of vaccines within 4-24 weeks after the 1st dose. Further, a new trend of HBV therapy is depend upon understanding the mechanism of HBV infection and immunity, where require appropriate animal model because of the strict host restriction of HBV infection. It is imperative to establish a mouse model that can precisely simulate HBV infection in humans and is convenient for anti-HBV drug and vaccine evaluation. HBV transgenic animals have proven very useful in some immunological studies, but always develop immune tolerance to the dominant HBV antigens (Chisari, 1996; Guidotti and Chisari, 2006). Additionally, the lentiviral backbone-based transfer vectors was found to be more readily establish persistent HBV infection in mouse models via Hydrodynamic Injection (HDI), providing a new tool useful for the study of HBV infection and immune-based therapies (Chuai *et al*., 2014)

HCV management: Interferon α (IFNα) and/or β are currently the most effective agents for treatment of chronic hepatitis C virus. The mathematical of HCV inhibition during IFN-α treatment including 2 conflicting hypothesis, i.e., inhibition of de Novo infection of susceptible cells by Zeuzem *et al*. (1996) and blocking of viral production or release by Neumann *et al*. (1998). As well as, interferon β-treatments are as effective as IFN-α in which, the IFN-β and 1FN-α share the same receptor and intracellular pathway (Kakumu *et al*., 1993). In contrast, other study suggested that a 2nd receptor-associated protein is specifically involved in the 1FN-β signaling pathways (Platanias *et al*., 1994). Viral decay slope, half-life, production and clearance of HCV-RNA after first administration of IFN-β were studied. Data obtained from Table 7, revealed that 15 of 49 patients were not response. Unvariate analysis indicated that low pretreatment serum HCV-RNA levels and simple diversity of HVR were factors associated with Sustained Responses (SR). The calculated viral decay slope during 24 h after 1st administration of IFN-β ranged from 2 to 6 with a Mean±SE of 2.63±1.28 (Fukutomi *et al*., 2001). Likewise, the monotherapy with interferon alpha (IFN-α) achieves a virologic end of 'treatment response in approximately 30-50% of patients with chronic hepatitis C virus has been reported. After discontinuation of treatment, however, a considerable proportion of patients relapse and sustained virologic response rates 24 weeks after the end of treatment are generally less than 20%. Recent studies showed the benefit of adding the synthetic guanosine nucleotide analog ribavirin to IFN-α. End of treatment and sustained virologic response rates in patients treated with IFN-α plus ribavirin for 48 weeks are approximately 50 and 40%, respectively (Sarrazin *et al*., 2000). In general, liver cirrhosis and hepatocellular carcinoma are associated with Hepatitis C Virus (HCV) in some cases of infected people. Although, various immunotherapies against the progressive disease status of HCV infection have been studied. The use of DNA vaccine is an attractive approach for generating antigen-specific immunity to various pathogens because of its stability and simplicity of delivery. However, many studies on DNA vaccines against HCV infection have been performed in mouse systems (Youn *et al*., 2003; Masalova *et al*., 2010). Ultimately, the DNA vaccines, especially that expressing the non-structural protein gene, may be an alternative approach for treatment of individuals chronically infected with HCV (Wada *et al*., 2013). Further, three major targets have reached evaluation in humans for chronic HCV infection (Farnik and Zeuzem, 2011): The NS3/4A serine protease, the large phosphoprotein NS5A and NS5B RNA-dependent RNA polymerase (RdRp) (Bobeck *et al*., 2010). The nucleoside analogs that target the HCV NS5B polymerase that have reached human clinical trials is the focus of recent studies in which they have broader activity against the various HCV GT and a higher barrier to the development of resistant viruses when compared to all other classes of HCV inhibitors (Coats *et al*., 2014).

Table 7: Clinical, virological and histological backgrounds of 49 patients in relation to the response to lFNβ treatment

Variables	SR(n = 15)	NR (In = 34)	p-value
Age (years)	45.3±15.1	51.0±10.5	0.2203"
Pretreatment HCV-RNA (copies/n.0)	103.2,3	187.1ii.-1	0.0005'
HCV genotype lb/2a/2b	3/10/2	16/12/6	0.1127'
Diversity of HVR			
Simple/complex	8/7	6/28	0.0172'
Liver histology			
Grading (mild/moderate/severe)	12/3/0	19/9/6	0.1509[c]
Staging (mild/moderate/severe)	71711	10/15/9	0.2336'

[a]Mean±SD, [b]Mann: Whitney test, [c]Fisher's exact probability test after Fukutomi *et al*. (2001)

FOOD TOXINS

Biogenic amines

Occurrence of biogenic amines in miscellaneous foods: Biogenic Amines (BA) are organic, basic, nitrogenous compounds with biological activity, mainly formed by the decarboxylation of amino acids. BA are present in a wide range of foods, including dairy products and can accumulate in high concentrations. In some cheeses more than 1000 mg of BA have been detected kg^{-1} of cheese. The consumption of food containing much amounts of these amines can have toxicological consequences. Although, there is no specific legislation regarding the BA content in dairy products, it is generally

assumed that they should not be allowed to accumulate. The most important BA in dairy foods are histamine, tyramine which produced by enzymatic decarboxylation of histidine and tyrosine, respectively, putrescine (synthesized via ornithine decarboxylation or agmatine deamination) and to a minor extent, cadaverine that originated by lysine decarboxylation. These amino acid decarboxylating activities are mainly attributable to the microbial groups that participate in the fermentation process, e.g., the content of semi-soft cheese of biogenic amines was found to associate with microbial groups of Enterobacteriaceae and Enterococci (Schneller *et al*., 1997). Further, the formation of biogenic amines during feta cheese ripening was investigated. The total biogenic amines content in mature cheese (60 days) was 330 mg kg^{-1}. Tyramine and putrescine were the main biogenic amines, while tryptamine and phenylethylamine were found in a low concentration (Valsamaki *et al*., 2000). Another investigation determined the relationship between commercial starter and biogenic amines formation during goat cheese ripening.Putrescine, tryptamine and tyramine (94.5 mg kg^{-1}) were the dominant amines (Novella-Rodriguez *et al*., 2002). On the other side, the effect of the hygienic quality of milk on the change of biogenic amines content and microbial count was investigated, by which the raw milk cheese showed a higher biogenic amines content compared to pasteurized milk cheese (Novella-Rodriguez *et al*., 2004). As well as, the biogenic amines content and microbial ecology of cheese were influenced by the type of milk used for cheese-making and by treatment applied to the raw materials (Lanciotti *et al*., 2007). Moreover, the content of biogenic amines were increased with the ripening period, especially in the edge part of cheese than in the core part, where the concentration of tyramine, histamine and putrescine were ranging from 5-392, 22-29 and 1-132 mg kg^{-1}, respectively (Komprda *et al*., 2008). Additionally, concerning milk-based fermented foods, cheese is the main product likely to contain potentially harmful levels of biogenic amines, especially tyramine, histamine and putrescine, however the processing technological aspects affecting BA biosynthesis and accumulation in dairy foods were studied.Improved knowledge of the factors involved in the synthesis and accumulation of BA is possible only when three conditions available (I) Presence of the substrate amino acids (ii) Presence of microorganisms (iii) Environmental conditions (Bunka *et al*., 2012; Linares *et al*., 2011, 2012. As well as, Biogenic amines are formed in fish and other food by microbial decarboxylation of amino acids. Some of biogenic amines like histamine, putrescine, cadaverine and tyramine are very important as a main cause of food intoxication and they also serve as chemical indicators of fish spoilage (Lehane and Olley, 2000; Kim *et al*., 2009). The presence of free histidine and the formation of histidine decarboxylase by certain bacterial species is responsible for histamine forming in fish (Kim *et al*., 2004). The histamine formation is a popular in the scombroid fish, i.e., tuna, bonito and mackerel. Another type of fish, i.e., herring, anchovies and mahi-mahi have also been concerned in outbreaks of biogenic amines (Huss *et al*., 2003).

Mackie *et al*. (1997) studied the biogenic amines content of the gonads of herring, mackerel and scallop and they found that the highest overall concentration of biogenic amines was in mackerel gonads and the lowest was in herring. Agmatine and spermine were present in mackerel gonads at concentrations higher than 20 mg 100 g^{-1}. The total amount of biogenic amines in the tested scallops was 9 mg 100 g^{-1}, which greater than that in the ovaries. However, histamine was absent in herring gonads and was at concentration of less than 1.0 mg 100 g^{-1} in the other species, where, histidine, the precursor of histamine was decreased during storage of herring muscle in ice or at 10°C. Additionally,the occurrence of histamine, putrescine, cadaverine and tyramine in different types of fish were also determined (Ayesh *et al*., 2012). Likewise, the formation ofputrescine and cadaverine in vacuum packed beef at chill temperature has been investigated (Edwards *et al*., 1985). The cadaverine concentration increased more rapidly than that of putrescine. Measurable increase of these biogenic amines were evident before maximum bacterial numbers were attained and before any permanent off odors were detected. Diamine concentrations were correlated better with the Total Viable Count (TVC) than that with counts of Gram-negative organisms. Fermented foods such as dry sausage were found to contain histamine along with other biogenic amines, the histamine formation mostly occurs during the 1st 2-4 weeks of sausage ripening at concentration of 100 mg/100 g sample. Where, *Lactobacillus buchneri* and other histidine decarboxylating microorganisms were responsible for histamine formation in fermented sausage (Stratton *et al*., 1991). Moreover, Cantoni *et al*. (1994) reported that the concentration of biogenic amines such as histamine, cadaverine, putrescine, tryptamine, spermidine and spermine increased during fermentation stage of Italian dry sausage. Hierro *et al*. (1999) found that the concentrations of putrescine, spermidine, spermine and β-phenylethyl amine was ranged in dry fermented sausages, from 0.1-1.4, 0.1-2.2, 6.3-9.8 and 0.3-1.2 mg kg^{-1}, respectively. While tryptamine, cadaverine, histamine and tyramine were not found.

Table 8: Effect of DEN on ATX transgenic and non-transgenic littermates*

Treatment	Transgene	Age (Mo)	Mice with foci' (% of group)		No. of foci (cm)		
					Total/group	Mean/group±SE	Mean foci radius (μm)
None	None	6-10	0/7	0	0		0
	ATX	6-10	0/13	0	0		0
DEN	None	6-10	14/16	88	318	21.2±4.0	349
	ATX	6-9	34/34	100	1052	36.3±3.7	386

*DEN was given as a single intraperitoneal dose 12-15 day-old mice, Foci observed upon microscopic examination of histological tissue section and scored as small, medium, or large after Slagle *et al.* (1996),

Table 9: Incidence of HCC in DEN-treated ATX and non-transgenic mice

Treatment	Transgene	No. of animals examined	Mice with HCC (% of group)
None	None	7	0
	ATX	13	0
DEN	None	16	4 (25)
	ATX	34	20(59)

After Slagle *et al.* (1996)

Table 10: Regulatory limits for histamine in fish

Parameters	Level (mg 100 g^{-1})		
	Hazard action	Defect action	Maximum allowable limit
USA (FDA)	50	10-20	-
EEC	-	-	20

After Huss (1994)

Physiological role and toxicological effects of biogenic amines: Biogenic amines have been involved as potentiators in hepatocarcinoma since Slagle *et al.* (1996) found that injection of mice with a single dose of Diethylnitrosamine (DEN) carrying HBV×protein causing hepatocarcinoma, which the hundred percent of DEN-treated AT×mice developed abnormal liver lesions, obtained data are showed in Table 8, 9 and Fig. 1. In addition, other biogenic amines, i.e., histamine, tyramine, tryptamine and β-phenylethylamine were found to be biologically psycho and/or vaso active in human (Lovenberg, 1973). Likewise, migraine attacks and hypertensive crises were associated with food containing tyramine in patient treated with monoamine oxidase inhibitors. Scombroid poisoning is one of the popular intoxication associated with fish meal containing high levels of histamine (Le Jeune *et al.*, 1995). Huss (1994). reported that facial flushing, urticaria, edema and gastrointestinal tract are clinical symptoms associated with consumption of histamine containing foods. Food and Drug Administration (FAD) has demonstrated the crucial limit of histamine (Table 10), that should not be exceeded in food commodities and these crucial limits not be absolute, in which the immune system responses are different from somebody to another. Moreover, histamine N-methyltransferase and monoamine oxidase are endogenous enzymes of intestine, which destroy both of histamine and other biogenic amines. Meanwhile, other studies pointed out that the alcoholic beverage, high levels of amines and antidepressant drugs were inhibitors, for those enzymes (Askar and Treptow, 1986). On the other hand, it has been reported that histamine exert its toxic effect by interacting with receptors on cellular membrane and both of H1 and H2, of histamine receptors were found in human and other species (Joosten, 1988). In contrast, Lovass (1991) pointed out that polyamines include spermine, spermidine and putrescine have a role in free radicals scavengers. Additionally, they play a vital role in maintaining the metabolic activity of normal function of immunological system of gut and implicated in evolution of intestinal tissues (Romain *et al.*, 1992) Whilst, catecholamine, indolamine and histamine have important function in human especially in the control of blood pressure and serving as primary mediator of the immediate symptoms in allergic responses (Santos, 1996). In recent studies as described by El-Hersh (2002) as shown in Fig. 2 pointed out that intraperitoneally injection of 100 μmol kg^{-1} (mice body weight) of histamine, cadaverine or putrescine led to decrease in Haemoglobin (Hb) and Red Blood Cells (RBC's), whilst White Blood Cells (WBC's) were increased. Additionally, alanine amino transferase (ALT) and aspartate amino transferase (AST) were also increased as a result of injection of aforementioned amines (Fig. 3). Contrarily, serum albumin was decreased. Moreover, the histopathological studies showed that lymphocytic infiltration and hepatic inflammation of liver as a result of mice injection with 100 μmol kg^{-1} putrescine (Fig. 4), while a mixture of tested biogenic amines caused lymphocytic infiltration around the central vein with intact liver architecture (Fig. 5).

In eukaryotic cells, BA biosynthesis is essential, as these compounds function as precursors for the synthesis of hormones, alkaloids, nucleic acids and proteins (Premont *et al.*, 2001). Some BAs have an important role as neurotransmitters, whereas others, such as putrescine and spermidine, are needed for critical biological functions (Igarashi *et al.*, 2001). In prokaryotic cells, the physiological role of BA synthesis mainly seems to be related to defense mechanisms used by bacteria to withstand acidic environments (Rhee *et al.*, 2002; Lee *et al.*, 2007). Decarboxylation increases survival under acidic stress conditions (Rhee *et al.*, 2002) through the consumption of protons and the excretion of

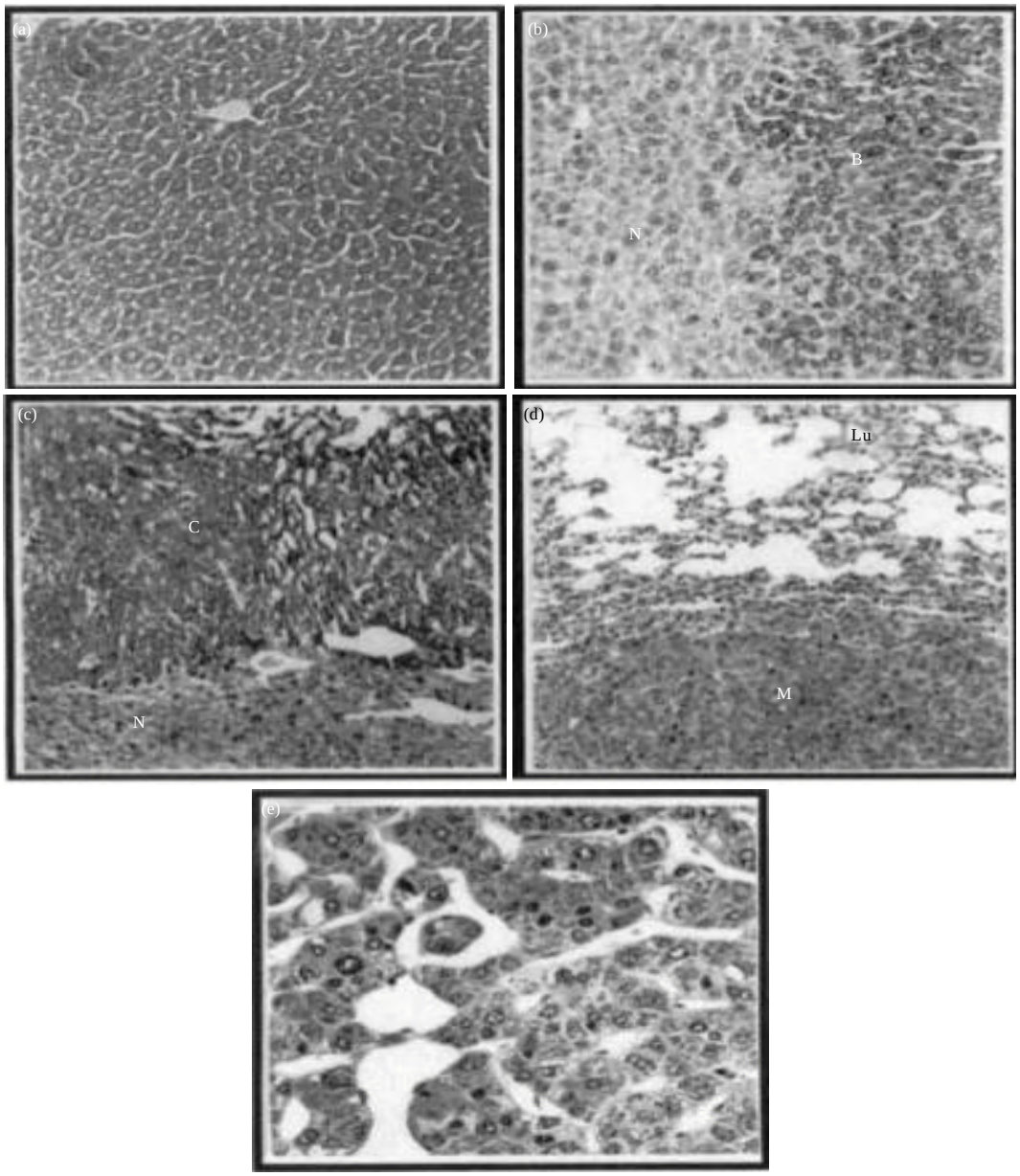

Fig. 1(a-e): Histological analysis of formalin-fixed liver tissues from diethylnitrosamine (DEN)-treated and control mice. Sections were cut from paraffin blocks and stained with hematoxylin and eosin. Shown are representative results from (a-b) Untreated transgenic mice harboring the X gene (ATX) mouse, 6-mo-old DEN-treated ATX mouse, (c) 8-mo-old DEN-treated ATX mouse and (d) Lung tissue from a 10-mo-old DEN-treated non-transgenic mouse. In panel B, note the cluster of smaller basophilic cells (labeled B) that are contiguous with normal hepatocyte, (labeled N). The architecture of the cords is preserved. In panel C, a hepatocellular carcinoma (labeled C) is compressing the adjacent liver (labeled N). There is significant architectural distortion and cellular pleomorphism and mitotic activity. In panel D, the metastasis (labeled M) to the lung (labeled Lu) has the same degree of hepatocellular differentiation as the primary tumor. (e) Hepatocellular carcinoma (HCC) in an 8-mo-old DEN-treated ATX mouse (x400). It is a well-differentiated carcinoma growing in multicellular cords and displaying moderate nuclear pleomorphism. The premalignant and hyperplastic foci of proliferation have the usual thickness of hepatic plates and uniform nuclei. After Slagle *et al*. (1996)

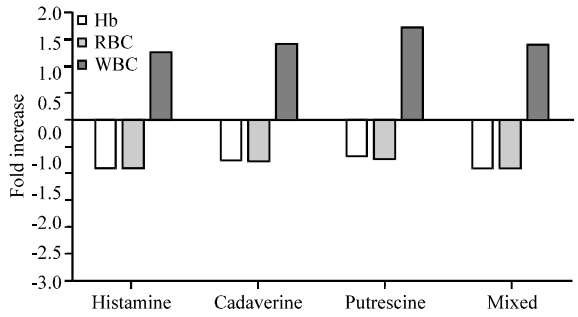

Fig. 2: Fold increase and decrease of haemoglobin (Hb), red blood cells (RBC's) and white blood cells (WBC's) as affected by 100 μmol of tested amines either separately or mixed, injected to swiss albino mice. After El-Hersh (2002)

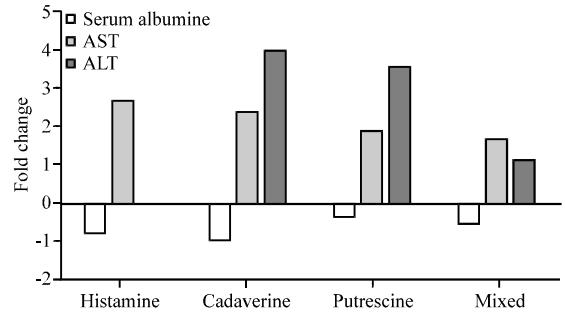

Fig. 3: Fold increase and decrease of serum albumin, Aspartate Amino Transferase (AST) and Alanine Amino Transferase (ALT) as affected by 100 μmol of tested amines either separately or mixed, injected to swiss albino mice. After El-Hersh (2002)

amines and CO_2, helping to restore the internal pH (Van de Guchte *et al*., 2002). BA production may also offer a way of obtaining energy: Electrogenic amino acid/amine antiport can lead to generation of proton motive force (Molenaar *et al*., 1993). This function would be particularly important for microorganisms lacking a respiratory chain for generating high yields of adenotriphosphate (Vido *et al*., 2004). Some studies suggest new and interesting hypotheses on the physiological role of amines in microorganisms (Tkachenko *et al*., 2001).

In *Escherichia coli*, the expression of oxyR, the gene that protects *E. coli* against oxidative stress, was enhanced by physiological concentrations of the BA, putrescine. Moreover, putrescine was shown to produce a protective effect if the DNA is damaged by reactive oxygen species (Tkachenko *et al*., 2001). Cells of *E. coli*

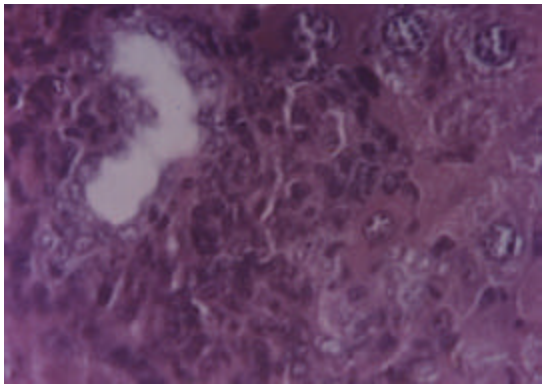

Fig. 4: Photo-micrograph showing lymphocytic infiltration and hepatic inflammation of mice liver injected with 100 μmol of putrescine. After El-Hersh (2002)

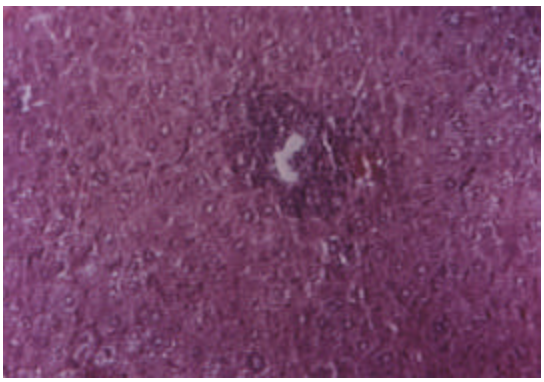

Fig. 5: Photo-micrograph showing lymphocytic infiltration around the vein with intact liver architecture as a result of injection with mixture of biogenic amines. After El-Hersh (2002)

grown in M9 minimal medium and subjected to a hyperosmotic shock by addition of 0.5 M NaCl immediately started to excrete putrescine, suggesting that putrescine may be involved in osmotic stress tolerance in *E. coli*. Therefore, bacteria that possess amino acid decarboxylase activity could overcome or reduce the effects of factors that induce stress responses in the cell, such as oxygen and NaCl, with the production of BA. Although, BA is required for many critical biological functions, the consumption of foods containing large amounts of BA can have toxicological consequences. After food consumption, small quantities of BA are commonly metabolized in the human gut to physiologically less active forms through the action of

amine oxidases (monoamine oxidases (MAOs) and diamine oxidase). Histamine can also be detoxified by methylation (through the action of methyl transferases) or acetylation (Lehane and Olley, 2000). However, the intake of foods with high BA loads, or inadequate detoxification, either for genetic reasons (Caston *et al*., 2002) or because of the inhibitory effects of some medicines or alcohol (Bodmer *et al*., 1999), can lead to BA entering the systemic circulation and causing the release of adrenaline and noradrenaline, provoking gastric acid secretion, increased cardiac output, migraine, tachycardia, increased blood sugar levels and higher blood pressure (Shalaby, 1996). BA levels are also higher in patients with Parkinson's disease, schizophrenia and depression (Premont *et al*., 2001).

The establishment of what constitutes a toxic level of BA is difficult, as this depends on the characteristics of different individuals. Human sensitivity varies according to the individual detoxifying activities of some enzymes involved in BA metabolism, such as histamine methyltransferase or others less specific, such as MAO and diamine oxidase. These enzymes are inhibited by several types of drugs, such as the neuromuscular blocking drugs d-tubocurarine, pancuronium and alcuronium and ethanol (Sattler *et al*., 1985) or antidepressant drugs (Livingston and Livingston, 1996).

As a consequence of this synergistic action, the simultaneous consumption of fermented foods and beverages may cause disorders, including life-threatening serotonin syndrome, even if each separate product might not be considered as hazardous (Lonvaud-Funel, 2001). Because of the wide range of possible monoamine oxidase inhibitor (MAOI) drug and tyramine-rich food interactions, the use of MAOIs has been limited, despite their clinical benefits (Livingston and Livingston, 1996). This risk has also prompted clinicians to propose the so-called 'MAOI diet', in which the tyramine intake is controlled by restricting known tyramine-rich food stuffs corresponding mainly to fermented products (aged cheese; aged or cured meats; sauerkraut; soy sauce and tap beer) (Gardner *et al*., 1996). Secondary amines, such as putrescine and cadaverine, can also react with nitrite to form carcinogenic nitrosamines (Brink *et al*., 1990) and the adherence to intestinal mucosa of some enteropathogens, such as *E. coli* O157:H7, is increased in the presence of tyramine (Lyte, 2004). It has been suggested that BAs have been the causative agents behind a number of food poisoning episodes, the most notorious being caused by histamine. Histamine poisoning is also known as 'scombroid poisoning' owing to the association of this illness with the consumption of scombroid fish (Taylor, 1983).

With respect to cheese, BA food poisoning can be caused by high levels of tyramine, especially in combination with the use of MAOIs as antidepressants. This effect is known as the 'cheese reaction' (Santos, 1996). There is little specific legislation with regard to BA content in foods. Although for fish products there are clear limits for histamine Commission Regulation (EC) 2073/2005), upper limits for BA in other foods have only been recommended or suggested (for example, 100 mg of histamine kg^{-1} of food or 2 mg of histamine L^{-1} of alcoholic beverage).

Generally, in alcoholic beverages, the toxic dose is considered to be between 8 and 20 mg L^{-1} for histamine, 25 and 40 mg L^{-1} for tyramine, whereas as little as 3 mg L^{-1} of phenylethylamine can cause negative physiological effects (Soufleros *et al*., 1998).

In addition to toxicological effects, BA in wine can also have consequences for wine retailers trying to export wines, as some countries have established maximum limits for histamine content in wine (Martin-Alvarez *et al*., 2006).

Alcoholic beverages

Alcoholic hepatitis: Alcoholic Hepatitis (AH) is a toxic liver disease resulting from excessive alcohol use. Although the clinical spectrum of the diseases includes both non-icteric and icteric presentations, an estimated mortality with more than 50% occurs in severe forms of icteric AH (Morgan, 1996). Moreover, AH even as a mild non-icteric disease, predisposes to the development of cirrhosis. Due to continued use of alcohol in most cultures, AH remains a significant public health problem. Diagnosis of AH is routinely assessed by liver biopsy, which characteristically shows ballooning degeneration of hepatocytes, mallory bodies and neutrophil infiltrates (Orrego *et al*., 1983). Treatment of AH usually consist of stopping drinking and corticosteroid therapy in severe forms (Ramond *et al*., 1992). However, this severe liver injury remains a therapeutic challenge. Better knowledge of the mechanism of hepatocyte death in AH is important to understand alcoholic liver disease and develop specific therapeutic strategies. Theoretically, hepatocyte death can occur by either apoptosis or necrosis. In addition, apoptotic hepatocyte can be morphologically recognized on liver biopsies as acidophilic bodies, which are detached from surrounding tissue, cytoplasmic and nuclear shrinkage and chromatin condensation. *In vivo* and *in vitro* studies suggested that the mechanism for alcohol-induced apoptosis includes the effect of oxidative stress or cytokine such as tumor necrosis factor-α (TNF α) on glutathione depleted hepatocytes.

Recent studies, pointed out that, tunnel and caspase-3-positive hepatocytes were observed in the

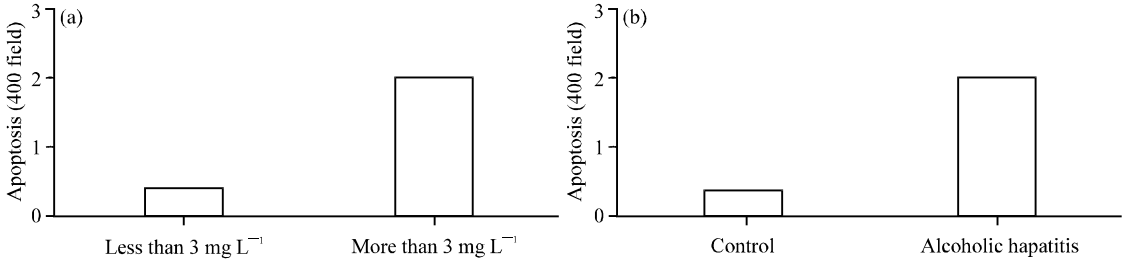

Fig. 6(a-b): Apoptosis associated with (a) Bilirubin and (b) Alcoholic hepatitis after Natori *et al*. (2001)

livers of patients with AH. In addition, in AH group, hepatocyte apoptosis was significantly higher in patients with a serum bilirubin of >3 mg dL^{-1} (Fig. 6). Apoptosis was also greater in grade 4 steatohepatitis (Natori *et al*., 2001).

CONCLUSION

Hepatitis B and C viruses are major etiologic agents of acute and chronic viral hepatitis especially in many developing countries. Diagnosis ofboth HBV and HCV based on serological detection of anti-HBV and anti-HCVantibodies by ELISA and Recombinant Immunoblot Assay that showed to be less accuracy in which, some patients despite testing negative for hepatitis B surface antigen (Anti HBVIgm), had detectable HBV DNA in serum polymerase chain reaction. Cytotoxic T lymphocyte (CTL) response play a crucial role in treatment of HBV, in which the lamivudine (3TC) course treatment can restore CTL susceptible to exogenous stimulation. As well as, immunization of hepatitis B infected patients with pre-s1/pre-s2/s play a crucial role in the treatment of HBV patients. On the other hand, interferon α and β are currently the most effective agents for treatment of chronic hepatitis C virus and the mathematical of HCV inhibition during IFN-α treatment including conflicting hypothesis, i.e., inhibition of de Novo infection of susceptible cells and blocking of viral production or release. As well as, interferon β-treatments was found as effective as IFN-alpa in which the IFN-β and IFN-α share the same receptor and intracellular pathway.

However, On the other hand, food toxins were found to play a vital role in sustain the viral infection, as well as,the toxins have a crucial role in hepatocarcinoma, since, the single dose of 2 μg g^{-1} b.wt. of diethylnitrosamine (DEN) enhanced hepatocarcinoma in mice carrying the hepatitis B virus×gene. Moreover, other biogenic amines, i.e., histamine, cadaverine or putrescine causing hepatocyte inflammation and lymphocyte infiltration during injection of 100 μmole in mice. On the other side, Alcoholic Hepatitis (AH) is atoxic liver disease resulting from excessive alcohol use, in which the clinical spectrum of the diseases includes both non-icteric and icteric presentation with estimated mortality more than 50% occur in severe forms of icteric AH. Diagnosis of AH is routinely assessed by liver biopsy, which characteristically shows ballooning degeneration of hepatocytes, Mallory bodies and neutrophil infiltrates.

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