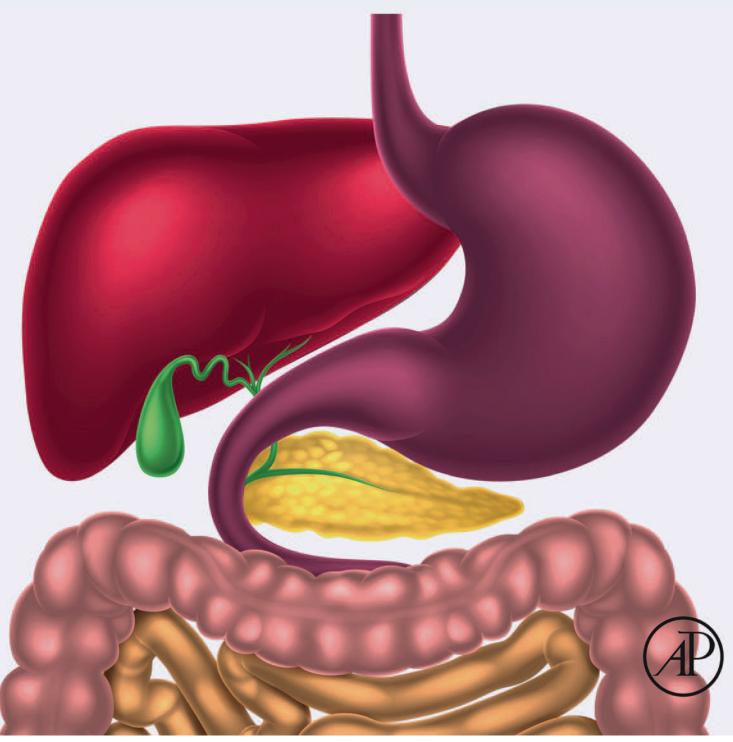
Dietary Interventions in Liver Disease

Foods, Nutrients, and Dietary Supplements

Edited by Ronald Ross Watson and Victor R. Preedy



Dietary Interventions in Liver Disease

Foods, Nutrients, and Dietary Supplements

Edited by

Ronald Ross Watson Victor R. Preedy





Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Copyright © 2019 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

ISBN: 978-0-12-814466-4

For information on all Academic Press publications visit our website at https://www.elsevier.com/books-and-journals



Publisher: Stacy Masucci

Acquisition Editor: Stacy Masucci

Editorial Project Manager: Megan Ashdown

Production Project Manager: Punithavathy Govindaradjane

Cover Designer: Mark Rogers

Typeset by TNQ Technologies

Contents

List of Contributors	XV	2.3 Alcoholic Fibrosis	16
Acknowledgments	xix	2.4 Alcoholic Cirrhosis	17
		3. Current Therapies for Alcoholic	
		Liver Disease	17
Section I		3.1 Abstinence and Lifestyle	
Overview of Liver Health		Modification	17
Overview of Liver Fleatur		3.2 Nutritional Support and	
1 Conomo Bosod Nutvition in Chronic		Supplements	17
1. Genome-Based Nutrition in Chronic		3.3 Pharmacological Drugs and	
Liver Disease		New Agents That Are Under	
Camia Dannan Jamid Dinana Jairana		Development	17
Sonia Roman, Ingrid Rivera-Iñiguez,		3.4 Liver Transplantation	20
Claudia Ojeda-Granados,		3.5 Natural and Herbal Medicines for	
Maricruz Sepulveda-Villegas and Arturo Panduro		the Prevention and Treatment of ALD	20
and Arturo Fanduro		3.6 Herbal Formulas for Treatment	2.0
1. Introduction	3	of Alcoholic Liver Disease	20
1.1 Chronic Liver Disease	3	3.7 The Combination Therapies	2.5
1.2 Hepatopathogenic Diet and Its		of Drugs and Natural Agents	25
Variations by Liver Disease Etiology	3	Endnotes	25 25
2. Genome-Based Nutrition:		References	23
A Regionalized and Personalized Diet	4	2 Features of Hanatic Encophalanathy	
3. Genes, Microbiota, and Regionalized Diet	5	3. Features of Hepatic Encephalopathy	
4. Nutritional Intervention in Chronic	_	Mohamed M. Amin	
Liver Disease	5	Monamed W. Allin	
4.1 Nonalcoholic Fatty Liver Disease—	-	1. Introduction	31
Nonalcoholic Steatohepatitis	6	2. Pathogenesis	31
4.2 Alcoholic Liver Disease	8	2.1 Ammonia Assumption	31
4.3 Hepatitis C Virus Infection	9	2.2 Gamma-Aminobutyric	
5. Concluding Remarks List of Abbreviations	11 11	Corrosive Assumption	32
Glossary	12	2.3 Changeability of Hepatic	
References	12	Encephalopathy	32
References	12	3. Clinical Features of Hepatic	
2. Current Therapeutic Strategies		Encephalopathy	32
for Alcoholic Liver Disease		4. Laboratory Irregularities in	0.0
for Alcoholic Liver Disease		Hepatic Encephalopathy	33
Alas El Dia El Causad El Cisi		5. Regular Precipitants of Hepatic	20
Alaa El-Din El-Sayed El-Sisi,		Encephalopathy	33
Samia Salim Sokar and		6. Distinguishable Diagnosis for	2
Dina Zakaria Mohamed		Hepatic Encephalopathy	34
1. Introduction	15	7. Controlling of Hepatic Encephalopathy	34
2. Pathogenesis of Alcoholic Liver Disease	16	7.1 Methodology Respects	34
2.1 Alcoholic Fatty Liver (Steatosis)	16	7.2 Medications to Decrease	3 /
2.2 Alcoholic Henatitis	16	Intestinal Ammonia Production	34

	7.3 Measurements to Upregulate		2.1 The Ubiquitin–Proteasome	
	Ammonia Clearance	36	System	59
	7.4 Medicines to Improve Sleep		2.2 Autophagy	60
	Disturbances	37	2.3 Crosstalk Between the UPS	
	7.5 Post–Transjugular Intrahepatic		and Autophagy	60
	Portosystemic Shunt Hepatic		3. ROS and Intracellular Proteolysis	61
	Encephalopathy	37	3.1 Inhibition of UPS by ROS	61
	8. Insignificant Hepatic Encephalopathy	37	3.2 Inhibition of Autophagy by ROS	61
	References	37	4. The Interconnection of ROS,	٠.
	References	37	Intracellular Proteolysis, and NAFLD	63
1	The Liver Before and After Bariatric		4.1 Nonalcoholic Fatty Liver	03
т.			Disease	63
	Surgery		4.2 Oxidative Stress and NAFLD	63
			4.3 Impaired Intracellular	03
	Flavio A. Cadegiani		Proteolysis in NAFLD	63
	1. Introduction: The Liver of the		4.4 Multiple Mechanisms of	03
	Obese Patient	39	·	
	1.1 Biochemical Markers and		Autophagic Dysfunction	<i>C</i> 1
	Alterations of the Liver in Obesity	39	in NAFLD	64
	1.2 Gene Expressions and Polymorphisms	00	4.5 Upregulation of Rubicon	
	in the Sick Liver of the Obese	42	in NAFLD	65
	1.3 The Challenging Management of	12	5. Conclusion Remarks	66
	NAFLD, NASH, Liver Fibrosis, and		References	66
	Cirrhosis in Obesity	42		
	1.4 Preparation for Bariatric Surgery in	72		
	the Patient With Liver Dysfunction	42	Section II	
	2. The Liver After the Bariatric Surgery	45	Fruits Improve Liver Health	
	2.1 Methods of Analysis of the Liver	73		
	(Before and) After Bariatric Surgery	47	6. Polyphenols in the Management	
	2.2 Biochemical Markers of the Liver	47	of Chronic Liver Diseases	
		47		
	After Bariatric Surgery	47	Including Hepatocellular	
	2.3 Genes Expression After Bariatric	49	Carcinoma	
	Surgery	49		
	2.4 Liver Transplantation and Bariatric	50	Surendra Kumar Shukla and Vijay Kumar	
	Surgery 2.5 Liver Complications After Bariatric	30	1. Introduction	73
	·	52	2. Dietary Polyphenols in the	
	Surgery	32	Prevention of Chronic Liver Diseases	73
	2.6 Weight-Loss-Independent Effects of	гэ	3. Effect on Non-alcoholic Fatty Liver	
	Bariatric Surgery	52 5 2	Diseases	74
	3. Final Discussion	52 52	4. Effect on Nonalcoholic Steatohepatitis	75
	4. Conclusion	53	5. Effect of Polyphenols on Alcoholic Liver	, ,
	References	53	Diseases	<i>7</i> 5
_			6. Control of Hepatitis B Virus Infection	75
5.	Oxidative Stress and Dysfunction		7. Control of Hepatitis C Virus Infection	76
	of the Intracellular Proteolytic		8. Management of Hepatocellular	70
	Machinery: A Pathological		Carcinoma	76
	Hallmark of Nonalcoholic Fatty		9. Conclusions	76 76
	Liver Disease			
			List of Abbreviations	76 77
	Takujiro Homma and Junichi Fujii		Glossary References	77 77
			KOTOPOCOC	77
			References	
	Introduction Intracellular Proteolysis	59 59	References	

7.	Phytochemicals in the Prevention of Ethanol-Induced Hepatotoxicity:			ytotherapy for the Liver	
	A Revisit				
	Manjeshwar Shrinath Baliga, Arnadi Ramachandrayya Shivashankara, Sunitha Venkatesh, Harshith P. Bhat,		2.	Introduction Liver Disease Treatment Plant-Derived Compounds With Liver Beneficial Properties	101 101 101
	Princy Louis Palatty,		4	Curcuma longa	101
	Ganesh Bhandari and Suresh Rao		7.	4.1 Antiinflammatory Properties	102
	1. Introduction	79		4.2 Antifibrotic Properties	102
	2. Phytochemicals in the Protection	7 3		4.3 Anticancer Properties of	
	of Alcohol-Induced Hepatotoxicity	79		Curcumin	103
	2.1 Beta-Carotene	79		4.4 Antiheavy Metal Properties	
	2.2 Lutein	80		of Curcumin in the Liver	103
	2.3 Meso-Zeaxanthin	81		4.5 Antisteatotic Properties of	
	2.4 Betaine	81		Curcumin	103
	2.5 Ferulic Acid	82	5.	Silybum marianum	103
	2.6 Ellagic Acid	83		5.1 Antiinflammatory and	
	2.7 Epigallocatechin-3-Gallate	83		Immunomodulation Activities	104
	2.8 Quercetin	84		5.2 Silymarin Prevents Fibrosis	104
	2.9 Morin	84		5.3 Beneficial Effects of Silymarin	104
	2.10 Hydroxystilbenes and Resveratrol	84		on NAFLD	104
	2.11 Ursolic Acid	85		5.4 Anticancer Properties of Silymarin	104
	2.12 Andrographolide and		6	Quercetin	104
	Arabinogalactan Proteins of	O.F.	0.	6.1 Quercetin Inhibits Liver	103
	Andrographis paniculata Nees 2.13 Picroliv	85 85		Inflammation	105
	2.14 Silymarin	85		6.2 Quercetin and Hepatic Fibrosis	105
	3. Mechanisms	86		6.3 Quercetin and Nonalcoholic	
	4. Conclusions	86		Steatohepatitis	106
	List of Abbreviations	86		6.4 Quercetin and Hepatocellular	
	References	87		Carcinoma	106
			7.	Naringenin	106
8.	Protective Actions of Polyphenols			7.1 Antiinflammatory Properties of	
	in the Development of			Naringenin	106
	Nonalcoholic Fatty Liver Disease			7.2 Naringenin Antifibrogenic Effects7.3 Naringenin and Hepatocellular	107
	Yoojin Lee and Ji-Young Lee		0	Carcinoma Coffee	107
	1. Introduction	91		Stevia	107 108
	2. Pathogenesis and Progression	<i>3</i> 1		Resveratrol	108
	of NAFLD	91		L-Theanine	108
	2.1 Liver Steatosis	91		Hesperidin	109
	2.2 Hepatic Oxidative Stress,			Colchicine	109
	Inflammation, and Apoptosis	92		Rosemary	109
	2.3 Liver Fibrosis	93		Glycyrrhizin (Glycyrrhizic Acid)	109
	3. Polyphenols in Foods and Natural			Other Plant-Derived Compounds	110
	Products	93	17.	Conclusions and Perspectives	110
	4. Protective Action of Polyphenols			Acknowledgments	114
	Against NAFLD Progression	94		References	114
	4.1 Quercetin	94			
	4.2 Epigallocatechin-3-O-Gallate	94			
	4.3 Anthocyanins	95			
	4.4 Resveratrol	95			
	5. Conclusion	96			
	References	96			

He	ction III erbs and Plants for Treating er Disease			6.	Conclusion List of Abbreviations References	141 141 142
10.	Curcuma longa, the Polyphenolic Curcumin Compound and		12.		e Flavone Baicalein and Its e in Gastrointestinal Disease	
	Pharmacological Effects on Liver			Yan	gchun Xie, Rui Kang and Daolin Tang	
	Bui Thanh Tung, Dong Thi Nham,			1.	Introduction	145
	Nguyen Thanh Hai and Dang Kim Thu				Extraction and Purification	145
	0 /	405			Metabolism and Conversion	145
	1. Introduction of <i>Curcuma longa</i>	125		4.	Use of Baicalein in Gastrointestinal	
	1.1 Chemical Composition in the	125			Disease	146
	Rhizome of <i>Curcuma longa</i> L. 2. The Polyphenolic Curcumin Compound	123 127				146
	2.1 The Therapeutic Potential	12/				146
	of Curcuma longa Components	127			1 , ,	146
	2.2 Antibacterial Activity	127				147147
	2.3 Antioxidant Activity	127			1 /	147
	2.4 Anti-inflammatory Activity	128				147
	2.5 For Treatment of Arthritis	128				147
	2.6 For Treatment of Metabolic	.20				148
	Syndrome	129			·	148
	2.7 For Treatment of Cancer	130		5	Mechanism of Action of Baicalein	148
	3. Curcumin and Liver Disease	131		Э.		148
	3.1 Curcumin Against Heavy Metals-				5.2 Regulation of Signaling	1 10
	Induced Liver Damage	131			9 9	149
	3.2 The Effects of Curcumin in			6.	Conclusion	151
	Preclinical In Vitro and In Vivo HCC	131		0.	Acknowledgments	151
	3.3 Hepatitis B Virus	132			References	151
	4. Conclusions	132				
	List of Abbreviations	132	13.	Pvi	rroloquinoline Quinone:	
	References	133			Profile, Effects on the Liver	
					d Implications for Health	
11.	Nymphaea alba and Liver				d Disease Prevention	
	Protection			uii	a Discuse i revention	
	Riham O. Bakr			Kare	en R. Jonscher and Robert B. Rucker	
	1. Introduction	125		1.	Introduction: Pyrroloquinoline	
	2. Traditional Uses	135 135			Quinone	157
	3. Phytoconstituents	136		2.	Factors Contributing to the	
	3.1 Flower Phytoconstituents	136		_	Development of NAFLD/NASH	161
	3.2 Leaf Phytoconstituents	136		3.	Systemic Effects of PQQ on	
	3.3 Rhizome Phytoconstituents	137			NAFLD/NASH	162
	4. Validated Studies	137			3.1 Mechanistic Modes of Action	162
	4.1 Hepatoprotective Effect of	.07			3.2 Pyrroloquinoline Quinone as an	160
	Flowers and a Powerful					162
	Anti-Inflammatory Activity	138			3.3 Pyrroloquinoline Quinone	162
	4.2 Leaf Extract and Potent Biological					162
	Activities	139			3.4 Pyrroloquinoline Quinone and Inflammation	165
	4.3 Rhizomes' Biological Activities	139			3.5 Pyrroloquinoline Quinone and the	103
	5. Phenolics of <i>N. alba</i> and Liver					165
	Protection	140			3.6 Pyrroloquinoline Quinone and	103
						166
					1 1010313	.00

	4.	Human Studies and Implications for			3.	Validated Uses	183
		Health	167		4.	Tea Protects Against the	
		4.1 Pyrroloquinoline Quinone and				Alcohol-Induced Hepatotoxicity	184
		Cognition	167		5.	Tea Protects Against Carbon	
		4.2 Pyrroloquinoline Quinone and				Tetrachloride-Induced Hepatotoxicity	185
		Skin Elasticity	167		6.	Effect of Tea on N-Acetaminophen-	
		4.3 Pyrroloquinoline Quinone and				Induced Hepatotoxicity	186
		Metabolism	168		7.	Tea Is Effective in Viral Hepatitis	186
	5.	Conclusions	168		8.	Effect of Tea on Ischemia-Reperfusion	
		References	168			Injury	186
					9.	Effect of Tea on Fatty Liver Disease	186
14.	He	rbal Weight Loss Supplements:				Effect of Tea on Hepatotoxicity of Lead	187
		om Dubious Efficacy to			11.	Effect of Tea on Hepatotoxicity	
		ect Toxicity				of Arsenic	187
	D	eet romeity			12.	Effect of Tea on Phenobarbitol-	
	Arm	nando E. González-Stuart and				Induced Liver Damage	187
		E O. Rivera			13.	Effect of Tea on Hepatotoxicity	
	J03C	. O. Rivera				of Microcystin	187
	1.	Introduction	175		14.	Effect of Tea on Hepatotoxicity	
	2.	The Surge of Herbal Product Use				of Aflatoxins	187
		Within Complementary and			15.	Effect of Tea on Hepatotoxicity of	
		Alternative Medicine	175			Azathioprine	188
	3.	The Internet as a Source of			16.	Effect of Tea on Galactosamine-	
		Information About Herbal Weight				and Lipopolysaccharide-Induced	
		Loss Supplements	176			Liver Damage	188
	4.	Herbal Supplement Identity,			17.	Effect of Tea on Hepatotoxicity	
		Efficacy, and Safety: Bedlam in the				of Insecticides	188
		Cyber Marketplace	176		18.	Effect of Tea on Hepatocarcinogenesis	188
	5.	Mexican Hawthorn Root	176			Conclusions	189
		5.1 Yellow Oleander or				List of Abbreviations	190
		"Codo de Fraile"	177			References	190
	6.	Toxicity of <i>Thevetia</i> spp.	177			References	130
	7.	Candlenut Tree Seed	178	16	НΔ	patoprotective Effects	
	8.	Botanical Characteristics	178	10.		the Indian Gooseberry (<i>Emblica</i>	
	9.	Use of the Candlenut Tree in					
		Asian Traditional Medicine	178		OII	icinalis Gaertn): A Revisit	
	10.	Weight Loss and Other Health			.,	· I CI · d D I·	
		Claims Made on the Internet for				njeshwar Shrinath Baliga,	
		Candlenut Tree Seeds	179			adi Ramachandrayya Shivashankara,	
	11.	International Health Agencies				Thilakchand, M.P. Baliga-Rao,	
		Ban Candlenut Seed Due to Its Toxicity	179			cy Louis Palatty, Thomas George	
	12.	Conclusions	179		and	Suresh Rao	
		References	180		1.	Introduction	193
					2.	Phytochemicals	193
15.	Tea	a (Camellia sinensis L. Kuntze)			3.	Traditional Uses	193
		Hepatoprotective Agent:			4.	Scientifically Validated Studies	194
		Revisit				Effect of Amla on Hepatotoxicity	
	/ L I	CVISIC				of Ethanol	195
	Arn	adi Ramachandrayya Shivashankara,			6.	Effect of Amla on Hepatotoxicity	
		esh Rao, Thomas George,				of Heavy Metals Arsenic and Cadmium	195
		iya Abraham, Marshal David Colin,			7.	Effect of Amla on Hepatotoxicity	
		rya Abraham, Marshai David Collil, Icy Louis Palatty and				of Iron Overload	196
		njeshwar Shrinath Baliga			8.	Effect of Amla on Hepatotoxicity	
	ivial	ijeshwai Sirinadi banga				of Ochratoxin	196
		Introduction	183		9.	Effect of Amla on Hepatotoxicity	
	2.	Phytochemistry of Tea	183			of Antitubercular Drugs	196

	10.	Effect of Amla on Hepatotoxicity				Bile Acids and Fiber	209
		of Hexachlorocyclohexane	196		17.	Prebiotics and Probiotics	209
	11.	Effect of Amla on Hepatotoxicity			18.	The Mediterranean and Other Diets	210
		of Carbon Tetrachloride	196		19.	Zinc	210
	12.	Effect of Amla on Hepatotoxicity			20.	Niacin (Nicotinic Acid)	210
		of Paracetamol	197		21.	Astaxanthin	210
	13.	Effect of Amla Phytochemicals			22.	Curcumin	210
		on Galactosamine- and			23.	Conclusion	210
		Lipopolysaccharide-Induced				References	211
		Liver Damage	197				
	14.	Effect of Amla Phytochemicals on		18.	The	e Effects of Dietary Advanced	
		Hepatotoxicity of Microcystin	197			cation End Products (AGEs)	
	15.	Effect of Amla on Hepatocarcinogenesis	197			Liver Disorders	
		Effect of Amla on Hepatic Lipid			OII	Liver Disorders	
		Metabolism and Metabolic Syndrome	198		Eshi	meh Agh and Farzad Shidfar	
	17.	Effect of Amla on Nonalcoholic			i aiii	men Agn and Farzad Smalar	
		Fatty Liver Disease	198		1.	Advanced Glycation End Products	21 3
	18.	Mechanism of Action(s) Responsible			2.	Circulating AGEs and Liver Disorders	215
		for the Hepatoprotective Effects	198		3.	The AGEs-RAGE System in Liver	
	19	Conclusions	199			Disorders	216
	13.	List of Abbreviations	199		4.	The Effects of Dietary AGEs on	
		References	200			Liver Disorders	218
		Further Reading	201			4.1 Liver Histology	218
		Turther Reading	201			4.2 Liver Enzymes	221
						4.3 Metabolic and Inflammatory	
C -	-4:-	11/				Profiles	221
		on IV				4.4 Reactive Oxygen Species	
Die	etar	y Macronutrients and				Production	222
		nutrients for Healthy Liver				4.5 Receptor for Advanced	
	ncti					Glycation End Products	223
ıuı	icu	OII				4.6 De Novo Lipogenesis	223
17	A 4 =	ion Diotom. Intomontions for				4.7 Weight Gain	224
1/.		jor Dietary Interventions for			5	Dietary Interventions to Reduce	22
	the	Management of Liver Disease			٥.	the AGEs	224
					6	Summary	224
	Idris	s Adewale Ahmed			0.	List of Abbreviations	227
	1	Introduction	205			References	228
		Liver as an Organ	206			References	220
		Liver Failure	206	10	110	lecular Mechanisms of the	
		Causes of Hepatic Injury	206	19.			
			206			tective Role of Wheat	
		Nonalcoholic Fatty Liver Disease				rm Oil Against Oxidative	
		Alcoholic Liver Disease	207		Str	ess-Induced Liver Disease	
	/.	Chronic Hepatitis B and Chronic	207				
	0	Hepatitis C	207		EI-S	ayed Akool	
		Hepatocellular Carcinoma	207		1	Introduction	222
	9.	Dietary Interventions in the	202			Introduction Reactive Overgen Species and	233
	4.0	Management of Liver Diseases	208		2.	Reactive Oxygen Species and	000
		Diet Types	208		•	Liver Diseases	233
		Fat	208		3.	Wheat Germ Oil and Liver Diseases	235
		Protein	208			3.1 Nutritional Composition	235
		Carbohydrates	208			3.2 Antioxidant Activity	235
	14.	Glycemic Index	209			References	236
		Antioxidants	209				

20.	Critical Role of Hepatic Fatty-Acyl Phospholipid Remodeling in Obese and Nonobese Fatty		2. Materials and Methods2.1 Drugs2.2 Study Design2.3 Induction of Acute Hepatotoxicity	258 258 258 258
	Liver Mouse Models		2.4 Statistical Analysis	258
			3. Results	259
	Walee Chamulitrat, Gerhard Liebisch,		4. Discussion	259
	Anita Pathil and Wolfgang Stremmel		References	260
	1. Introduction	239		
	1.1 Causes of Obesity: Genetics		22. The Role of Carbohydrate	
	and Diets	239	Response Element-Binding	
	1.2 Consequence of Obesity:		Protein in the Development	
	NAFLD and NASH	239	of Liver Diseases	
	1.3 Animal Models of Obese and		51 -11 51 - 10 51 51	
	Nonobese NAFLD/NASH	240	Katsumi lizuka	
	1.4 Comparison of Hepatic Lipids			
	Among Obese and Nonobese	0.44	1. Introduction	263
	NAFLD/NASH	241	2. ChREBP, a Glucose-Activated	
	2. Phospholipids in NAFLD and NASH	241	Transcription Factor That Regulates	262
	2.1 Linking Hepatic Triglyceride to	2.41	Glucose and Lipid Metabolism	263
	Phospholipid in NAFLD	241	3. Dietary Composition and ChREBP	263
	2.2 Comparison of Hepatic		4. ChREBP and Liver Diseases4.1 Nonalcoholic Fatty Liver Disease	264 264
	Phospholipid Among Obese and Nonobese NAFLD/NASH	241	4.1 Nonalconolic Fatty Liver Disease 4.2 Alcoholic Liver Disease	265
	2.3 Comparison of Hepatic	241	4.3 Liver Tumors	267
	Phospholipid Ratios Among		4.4 Virus Infection	267
	Obese and Nonobese		4.5 Glycogen Storage Diseases	268
	NAFLD/NASH	243	5. Supplement and ChREBP	268
	3. Phospholipid-Metabolizing Genes	243	5.1 Polyunsaturated Fatty Acids	268
	in Obesity and NAFLD	244	5.2 Ketone Bodies	269
	3.1 PLA2G6 or iPLA2β in Obesity		5.3 Vinegar (Acetic Acid)	269
	and NAFLD	245	5.4 Polyphenols	269
	3.2 Effects of iPLA2β Deficiency on		6. Conclusion	270
	Phospholipids in Obese Ob/Ob		Acknowledgments	270
	and HFD-Fed Mice	245	References	271
	3.3 Effects of iPLA2β Deficiency on			
	Phospholipids in MCD-Fed Mice	247	23. Trans Fatty Acid in the Liver	
	4. Summarized Findings and Proposed		and Central Nervous System	
	Mechanisms	247	,	
	5. Perspectives	251	Rafael Longhi	
	5.1 Use of iPLA2β Antagonists for		1. Introduction	275
	Steatosis Protection in Obese		2. Hydrogenation Process	275
	Versus Nonobese NAFLD	251	3. Biochemical Metabolism	276
	5.2 Considerations and Precautions	252	4. Trans Fatty Acids and Liver Damage	276
	6. Conclusions	252	4.1 Cell Culture	276
	List of Abbreviations	252	4.2 Animal Models	277
	Acknowledgments	253	4.3 Human Trials	279
	References	253	5. Trans Fatty Acids and the Central	
24	Vitamin D2 and Liver Bustantia		Nervous System	280
<i>Z</i> 1.	Vitamin D3 and Liver Protection		5.1 Animal Studies	281
	Malath Assos Al Cood		5.2 Human Trials	283
	Malath Azeez Al-Saadi		6. Final Considerations	284
	1. Introduction	257	References	284
	1.1 Mechanism of Action	257		

24.	Fish Oil Supplements During Perinatal Life: Impact on the Liver of Offspring		3.2 Functional Categories of Identified Hepatic Proteins of Diabetic Rats and Diabetic Rats With Purple Rice Bran Supplement	301
	Emilio Herrera and Encarnación Amusquivar		3.3 Bioinformatic Analysis of	301
	1. Introduction	287	Unique Proteins Found in the	
	2. Role of Fatty Acids in Fetal		Hepatic Tissues of Diabetic	
	Development	287	Rats and Diabetic Rats With	
	3. Fatty Acids and Epigenetics	288	Purple Rice Bran Supplement	303
	4. Fish Oil Supplements During	200	3.4 mRNA Expression Level of	
	Pregnancy 5. Provalence and Pathogonic Aspects	288	Candidate Genes of Diabetic	204
	5. Prevalence and Pathogenic Aspects of Nonalcoholic Fatty Liver Disease	290	Rats' Liver	304
	6. Fetal Programming Origins of NAFLD	290	3.5 mRNA Expression Level	304
	7. Potential Protective Role of Fish	230	of <i>Rangap1</i> Gene 3.6 mRNA Expression Level of	304
	Oil in the NAFLD Development	291	Candidate Genes of Purple	
	Acknowledgments	292	Rice Bran–Supplemented	
	References	292	Diabetic Rats' Liver	304
			3.7 mRNA Expression Level of	
25.	Purple Rice Bran Improves		Affected Genes From Hepatic	
	Hepatic Insulin Signaling via		Proteomic Analysis	304
	Activation of Akt and Stabilization		3.8 Protein Expression Level of	
	of IGF in Diabetic Rats		Affected Proteins From	
			Hepatic Proteomic Analysis	305
	Ei Ei Hlaing, Supicha Rungcharoenarrichit,		4. Discussion and Conclusion	305
	Narissara Lailerd, Sittiruk Roytrakul and		Acknowledgments	312
	Pichapat Piamrojanaphat		References Further Reading	312 312
	1. Introduction	297	ruttier keading	312
	2. Methods	298		
	2.1 Tissue Preparation and		Section V	
	Homogenization	298		
	2.2 Determination of Tissue Protein	200	Toxic Dietary Materials Including	_
	Concentration	298	Alcohol-Induced Liver Dysfunction	•
	2.3 One-Dimensional SDS-PAGE	298	Treatment	
	Analysis 2.4 In-Gel Tryptic Digestion Before	290		
	LC-MS/MS Analysis	298	26. Heavy Metals and Low-Oxygen	
	2.5 Peptide Identification and	230	Microenvironment—Its Impact	
	Quantitation by LC-MS/MS		on Liver Metabolism and Dietary	
	Analysis	299	Supplementation	
	2.6 Bioinformatics Analysis	299	W 1WD D: 111 ()	
	2.7 Confirmation of Candidate		Kusal K. Das, Rajesh Honnutagi,	
	Genes and Their Affected Proteins	299	Lata Mullur, R. Chandramouli Reddy, Swastika Das, Dewan Syed Abdul Majid	
	2.8 mRNA Level of Affected Genes by	200	and M.S. Biradar	
	Quantitative Real-Time PCR	300		
	2.9 Affected Protein Expression	300	1. Introduction	315
	Level by Western Blot Analysis 2.10 Statistical Analysis	300 300	2. Heavy Metals and Its Interactions	317
	3. Results	300	2.1 Heavy Metal Toxicities:	217
	3.1 LC-MS/MS Analysis and Hepatic	500	Nickel and Lead 3. Hypoxia Pathophysiology	317 318
	Proteins Identification	300	3.1 Hypoxia Microenvironment	318
			3.2 Hypoxia and Heavy Metals	510
			(Nickel and Lead)	318

 4. Heavy Metals in Liver Diseases 4.1 Heavy Metals and Liver Pathophysiology (Nickel and Lead) 4.2 Possible Mechanism of Altered 	319 319	28. Beneficial Effects of Natural Compounds on Heavy Metal-Induced Hepatotoxicity Parisa Hasanein and Abbasali Emamjomeh	
Hepatocellular Architecture by	221	1. Introduction	345
Heavy Metals	321	2. Arsenic Hepatotoxicity	346
5. Hypoxia and Liver Diseases	321	2.1 Mechanisms of Arsenic-Induced	340
5.1 Hypoxia—Liver Histopathology	322	Hepatotoxicity	346
5.2 Hypoxia and Heavy Metals (Nickel and Lead)—Liver		3. Cadmium Hepatotoxicity	346
(inicker and Lead)—Liver Histopathology	323	3.1 Mechanisms of Cadmium-	340
6. Heavy Metals (Nickel and Lead),	323	Induced Hepatotoxicity	347
Hypoxia, and Liver Functions—		4. Chromium Hepatotoxicity	347
Role of Dietary Supplementations	323	4.1 Mechanisms of Chromium-	0.,
6.1 Heavy Metals, Liver Functions,	323	Induced Hepatotoxicity	347
and Dietary Supplementation	324	5. Copper Hepatotoxicity	348
6.2 Hypoxia, Liver Function,	321	5.1 Mechanisms of Copper-Induced	
and Dietary Supplementation	324	Hepatotoxicity	348
6.3 Heavy Metals, Hypoxia,	32.	6. Lead Hepatotoxicity	348
and Liver Functions—Dietary		6.1 Mechanisms of Lead-Induced	
Supplementation	325	Hepatotoxicity	348
7. Conclusion	328	7. Mercury Hepatotoxicity	349
Acknowledgments	329	7.1 Mechanisms of Mercury-Induced	
References	329	Hepatotoxicity	349
		8. Effects of Natural Products on	
27. Cadmium and Fullerenes in		Heavy Metal-Induced Hepatotoxicity	350
Liver Diseases		8.1 Vitamins C and E	350
		8.2 Curcumin	350
Sinisa Djurasevic, Zoran Todorovic,		8.3 <i>N</i> -Acetylcysteine	350
Sladjan Pavlovic and Snezana Pejic		8.4 α-Lipoic Acid	351
	222	8.5 Melatonin	351
1. Introduction1.1 Cytochromes P450	333	8.6 Flavonoid-Rich Extracts	351
1.1 Cytochromes F430 1.2 Xenobiotic Metabolism and	333	8.7 Anthocyanidins	352
	334	8.8 Quercetin	352
Hepatotoxicity 2. Liver and Oxidative Stress	335	8.9 Naringenin	352
2.1 Oxidative Stress and	333	8.10 Black Tea	352
Liver Disorders	335	8.11 Olive Oil	352
3. Cadmium as the Model of	333	8.12 Sesame Oil	352
Hepatotoxicity	336	8.13 Combination Therapy References	352 353
3.1 Molecular Mechanisms	330	References	333
of Cadmium Toxicity	337	29. Nutritional and Dietary	
3.2 Cadmium and Oxidative Stress	337	Interventions for Nonalcoholic	
3.3 Cadmium and Liver Injury in			
Animals	338	Fatty Liver Disease	
3.4 Cadmium and Mitochondria	338	Cindu V. Coi Stalla Coulos	
4. Fullerenes and Liver Protection	338	Cindy X. Cai, Stella Carlos,	
4.1 Chemical Properties of Fullerenes	338	Pejman Solaimani, Bansari J. Trivedi, Chuong Tran and Shobha Castelino-Prabhu	
4.2 Pharmacological Properties of		Chuong Itali and Shobha Castellio-rtabilu	
Fullerenes	339	1. Introduction	357
4.3 Fullerenes as the Protectors		2. Epidemiology	357
in the Carbon Tetrachloride		3. Risk Factors	357
Model of Liver Toxicity	339	4. Pathogenesis	358
Acknowledgments	340	5. Clinical Manifestations	360
References	340	6. Histopathology	360

	7.	Diagnosis	360	4.	Hepatic Fructose Metabolism	374
	8.	Natural Course and Outcomes	361	5.	Fructose, the Common Etiological	
	9.	Treatment	361		Factor of NAFLD	374
		9.1 Lifestyle Modification for NAFLD	361	6.	Management of NAFLD	376
		9.2 Pharmacological Treatment	365	7.	Pharmacotherapy	376
		9.3 Bariatric Surgery and Endoscopic		8.	Lifestyle Intervention	376
		Bariatric Intervention	366	9.	Dietary Fat	376
	10.	Conclusions	366	10.	Metabolic Fate of n-3 Long-Chain	
		References	367		PUFA: Bioactive Lipid Mediators	378
				11.	Eicosapentaenoic Acid (EPA;	
30.	Die	etary Management of			C20:5n-3)-Derived Lipid Mediators	378
	No	nalcoholic Fatty Liver Disease		12.	Docosahexaenoic Acid (DHA;	
		AFLD) by n-3 Polyunsaturated			C22:6n-3)-Derived Lipid Mediators	378
		ty Acid (PUFA) Supplementation:		13.	n-3 PUFA and NAFLD	379
		Perspective on the Role of		14.	Lipid Mediators of n-3 PUFA	
		B PUFA-Derived Lipid Mediators			and NAFLD	382
	11-5	of Of A-Derived Lipid Mediators		15.	Conclusion	384
	CM	SM Jeyakumar and A Vajreswari			Acknowledgments	384
	SIVI ,	jeyakumai anu A vajreswan			References	384
	1.	Background	373			
	2.	NAFLD—Worldwide Burden	373	Index		391
	3.	Dietary Carbohydrates: A Glance				
		at Fructose	374			

List of Contributors

- **Soniya Abraham** Undergraduate student, Father Muller Medical College, Mangalore, India
- **Fahimeh Agh** Department of Nutrition, School of Health, Iran University of Medical sciences, Tehran, Iran
- **Idris Adewale Ahmed** Department of Biotechnology, Faculty of Science, Lincoln University College Malaysia, Petaling Jaya, Malaysia
- **El-Sayed Akool** Pharmacology and Toxicology Department, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt
- Malath Azeez Al-Saadi Basic Science\Pharmacology-Dentistry College, University of Babylon, Al-hilla, Babil, Iraq
- **Mohamed M. Amin** Department of Pharmacology, Medical Division, National Research Centre, Giza, Egypt
- **Encarnación Amusquivar** Department of Biochemistry and Chemistry, University San Pablo CEU, Madrid, Spain
- **Riham O. Bakr** Pharmacognosy Department, Faculty of Pharmacy, October University for Modern Sciences and Arts, Giza, Egypt
- **Manjeshwar Shrinath Baliga** Department of Research, Mangalore Institute of Oncology, Mangalore, India
- **M.P. Baliga-Rao** Department of Research, Mangalore Institute of Oncology, Mangalore, India
- **Ganesh Bhandari** Undergraduate student, Father Muller Medical College, Mangalore, India
- **Harshith P. Bhat** Mangalore Institute of Oncology, Mangalore, India
- M.S. Biradar Department of Medicine, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE Deemed to be University, Vijayapur, India
- Flavio A. Cadegiani Division of Endocrinology and Metabolism, Department of Medicine, Federal University of São Paulo, São Paulo, Brazil; Corpometria Institute, Centro Clínico Advance, Brasília, Brazil
- Cindy X. Cai Division of Gastroenterology and Hepatology, Department of Internal Medicine, VA Loma Linda Healthcare System, Loma Linda University, Loma Linda, CA, United States

- **Stella Carlos** Department of Nutrition Services, VA Loma Linda Healthcare System, Loma Linda, CA, United States
- **Shobha Castelino-Prabhu** Department of Pathology, VA Loma Linda Healthcare System, Loma Linda, CA, United States
- Walee Chamulitrat Department of Internal Medicine IV, University of Heidelberg Hospital, Heidelberg, Germany
- **Marshal David Colin** Undergraduate student, Father Muller Medical College, Mangalore, India
- **Kusal K. Das** Laboratory of Vascular Physiology and Medicine, Department of Physiology, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE Deemed to be University, Vijayapur, India
- **Swastika Das** Department of Chemistry, BLDE Association's, Dr. P.G. Halakatti College of Engineering and Technology, Vijayapur, India
- **Sinisa Djurasevic** University of Belgrade Faculty of Biology, Belgrade, Serbia
- **Alaa El-Din El-Sayed El-Sisi** Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tanta University, Tanta, Egypt
- **Abbasali Emamjomeh** Computational Biotechnology Lab (CBB), Department of Plant Breeding and Biotechnology (PBB), University of Zabol, Zabol, Iran
- **Junichi Fujii** Department of Biochemistry and Molecular Biology, Graduate School of Medical Science, Yamagata University, Yamagata, Japan
- **Thomas George** Undergraduate student, Father Muller Medical College, Mangalore, India
- **Armando E. González-Stuart** School of Pharmacy-University of Texas at El Paso, El Paso, TX, United States
- **Nguyen Thanh Hai** School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam
- **Parisa Hasanein** Department of Biology, School of Basic Sciences, University of Zabol, Zabol, Iran
- **Emilio Herrera** Department of Biochemistry and Chemistry, University San Pablo CEU, Madrid, Spain

- Ei Ei Hlaing Department of Biochemistry, Chiang Mai University, Chiang Mai, Thailand; Department of Biochemistry, University of Medicine, Mandalay, Myanmar
- Takujiro Homma Department of Biochemistry and Molecular Biology, Graduate School of Medical Science, Yamagata University, Yamagata, Japan
- Rajesh Honnutagi Department of Medicine, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE Deemed to be University, Vijayapur, India
- Katsumi Iizuka Department of Diabetes and Endocrinology, Graduate School of Medicine, Gifu University, Gifu, Japan; Gifu University Hospital Center for Nutritional Support and Infection Control, Gifu, Japan
- SM Jeyakumar Division of Lipid Biochemistry, National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India
- Karen R. Jonscher Department of Anesthesiology, University of Colorado Denver, Aurora, CO, United States
- **Rui Kang** Department of Surgery, University of Pittsburgh, Pittsburgh, PA, United States
- Vijay Kumar Department of Molecular and Cellular Medicine, Institute of Liver and Biliary Sciences, New Delhi, India
- Narissara Lailerd Department of Physiology, Chiang Mai University, Chiang Mai, Thailand
- Ji-Young Lee Department of Nutritional Sciences, University of Connecticut, Storrs, CT, United States
- Yoojin Lee Department of Nutritional Sciences, University of Connecticut, Storrs, CT, United States
- Gerhard Liebisch Institute of Clinical Chemistry and Laboratory Medicine, University of Regensburg, Regensburg, Germany
- Rafael Longhi Department of Basic Health Sciences, Federal University of Health Sciences of Porto Alegre (UFCSPA), Porto Alegre, Brazil
- Dewan Syed Abdul Majid Department of Physiology, School of Medicine, Tulane University, New Orleans, LA, United States
- Dina Zakaria Mohamed Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tanta University, Tanta, Egypt
- Lata Mullur Laboratory of Vascular Physiology and Medicine, Department of Physiology, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE Deemed to be University, Vijayapur, India
- Pablo Muriel Laboratory of Experimental Hepatology, Department of Pharmacology, Cinvestav-IPN, Mexico City, Mexico

- Dong Thi Nham School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam
- Claudia Ojeda-Granados Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara, "Fray Antonio Alcalde", Guadalajara, Mexico; Health Sciences Center, University of Guadalajara, Guadalajara,
- Princy Louis Palatty Department of Pharmacology, Amrita Institute of Medical Sciences, Kochi, India
- Arturo Panduro Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara, "Fray Antonio Alcalde", Guadalajara, Mexico; Health Sciences Center, University of Guadalajara, Guadalajara, Mexico
- Anita Pathil Department of Internal Medicine IV, University of Heidelberg Hospital, Heidelberg, Germany
- Sladjan Pavlovic University of Belgrade Institute for Biological Research "Sinisa Stankovic", Belgrade, Serbia
- Snezana Pejic University of Belgrade "Vinca" Institute of Nuclear Sciences, Belgrade, Serbia
- Pichapat Piamrojanaphat Department of Biochemistry, Chiang Mai University, Chiang Mai, Thailand
- Arnadi Ramachandrayya Shivashankara Undergraduate student, Father Muller Medical College, Mangalore, India
- Erika Ramos-Tovar Laboratory of Experimental Hepatology, Department of Pharmacology, Cinvestav-IPN, Mexico City, Mexico
- Suresh Rao Mangalore Institute of Oncology, Mangalore,
- R. Chandramouli Reddy Laboratory of Vascular Physiology and Medicine, Department of Physiology, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE Deemed to be University, Vijayapur, India
- Ingrid Rivera-Iñiguez Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara, "Fray Antonio Alcalde", Guadalajara, Mexico; Health Sciences Center, University of Guadalajara, Guadalajara, Mexico
- José O. Rivera School of Pharmacy-University of Texas at El Paso, El Paso, TX, United States
- Sonia Roman Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara, "Fray Antonio Alcalde", Guadalajara, Mexico; Health Sciences Center, University of Guadalajara, Guadalajara, Mexico
- Sittiruk Roytrakul National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency, Pathum Thani, Thailand

- Robert B. Rucker Department of Nutrition, University of California, Davis, CA, United States
- Supicha Rungcharoenarrichit Department of Biochemistry, Chiang Mai University, Chiang Mai, Thailand
- Samia Salim Sokar Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tanta University, Tanta, Egypt
- Maricruz Sepulveda-Villegas Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara, "Fray Antonio Alcalde", Guadalajara, Mexico; Health Sciences Center, University of Guadalajara, Guadalajara, Mexico
- Farzad Shidfar Department of Nutrition, School of Health, Iran University of Medical sciences, Tehran, Iran
- Surendra Kumar Shukla Eppley Cancer Institute, University of Nebraska Medical Centre, Omaha, NE, **United States**
- Pejman Solaimani Division of Gastroenterology and Hepatology, Department of Internal Medicine, VA Loma Linda Healthcare System, Loma Linda University, Loma Linda, CA, United States
- Wolfgang Stremmel Department of Internal Medicine IV, University of Heidelberg Hospital, Heidelberg, Germany
- Daolin Tang The Third Affiliated Hospital, Center for DAMP Biology, Key Laboratory of Protein Modification and Degradation of Guangdong Higher Education Institutes, School of Basic Medical Sciences,

- Guangzhou Medical University, Guangzhou, People's Republic of China; Department of Surgery, University of Pittsburgh, Pittsburgh, PA, United States
- K.R. Thilakchand Department of Research, Mangalore Institute of Oncology, Mangalore, India
- Dang Kim Thu School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam
- Zoran Todorovic University of Belgrade Faculty of Medicine, University Medical Center "Bezanijska kosa", Belgrade, Serbia
- Chuong Tran Division of Gastroenterology and Hepatology, Department of Internal Medicine, VA Loma Linda Healthcare System, Loma Linda University, Loma Linda, CA, United States
- Bansari J. Trivedi Department of Nutrition Services, VA Loma Linda Healthcare System, Loma Linda, CA, **United States**
- Bui Thanh Tung School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam
- A Vajreswari Division of Lipid Biochemistry, National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India
- Sunitha Venkatesh Mangalore Institute of Oncology, Mangalore, India
- Yangchun Xie Department of Oncology, The Second Xiangya Hospital of Central South University, Changsha, People's Republic of China; Department of Surgery, University of Pittsburgh, Pittsburgh, PA, United States

This page intentionally left blank

Acknowledgments

The work of Dr. Watson's editorial assistant, Bethany L. Steven, in communicating with authors, editors, and working on the manuscripts was critical to the successful completion of the book. It is very much appreciated. Support for Ms. Stevens' and Dr. Watson's editing was graciously provided by Southwest Scientific Editing & Consulting, LLC. Direction and guidance from Elsevier staff was critical. Finally, the work of the librarian at the Arizona Health Science Library, Mari Stoddard, was vital and very helpful in identifying key researchers who participated in the book.

Heavy Metals and Low-Oxygen Microenvironment—Its Impact on Liver Metabolism and Dietary Supplementation

Kusal K. Das¹, Rajesh Honnutagi², Lata Mullur¹, R. Chandramouli Reddy¹, Swastika Das³, Dewan Syed Abdul Majid⁴, M.S. Biradar²

¹Laboratory of Vascular Physiology and Medicine, Department of Physiology, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE Deemed to be University, Vijayapur, India; ²Department of Medicine, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE Deemed to be University, Vijayapur, India; ³Department of Chemistry, BLDE Association's, Dr. P.G. Halakatti College of Engineering and Technology, Vijayapur, India; ⁴Department of Physiology, School of Medicine, Tulane University, New Orleans, LA, United States

1. INTRODUCTION

The **term heavy** metal refers to any metallic chemical element that has a relatively high density and is toxic or poisonous at low concentrations. The heavy metals constitute major fraction of the periodic table and are generally interpreted to include those metals from periodic table groups IIA through VIA. Examples of heavy metals are nickel, lead, mercury, cadmium, chromium, etc. Heavy metals cannot be degraded or destroyed. It enters in our bodies via food, drinking water, and air and primarily targets liver and other metabolically active tissues. As trace elements, some heavy metals (e.g., copper, selenium, zinc) are essential to maintain the metabolism of the human body. However, at higher concentrations they can lead to poisoning. Heavy metal poisoning may occur through various ways such as drinking water through lead pipe or occupational exposure (lead-cadmium or nickel-cadmium batteries) or stainless steel industries (nickel-chromium), refineries or petrochemicals (nickel, lead, cadmium), jewelry, etc. 1 Hypoxia belongs to the most serious factors that can directly impair the function of metabolic pathways in the animal cell. The exposure of experimental animals to hypoxia has been widely used in many morphological and physiological studies. Physiological hypoxia induces cell signaling process for the formation of new blood vessels (angiogenesis) to regulate vascular tone during developmental stage. Physiological oxygen levels (PO₂) in healthy body varies from -100 Torr in the alveoli to <10 Torr in medulla of kidney and retina.³ Tissue exposure to low-oxygen tension is observed in several physiological and pathological conditions such as ischemia for shorter duration or in case of the high-altitude inhabitants or any other chronic diseases for longer duration of hypoxic exposure. In both cases, hypoxic cells are programmed to rapid adjustment to maintain O₂ supply to most vital organs such as heart and brain. It is understood that atherosclerosis, stroke, or vascular occlusion leads to tissue ischemia followed by hypoxia. Tissue hypoxia also develops through immune cell infiltration in vascular dysfunction during chronic inflammation process.^{3,4} It has been observed that hypoxia absurdly stimulates free radicals release from the mitochondria that control the transcriptional and posttranslational response to low-oxygen conditions. Hypoxia-induced generation of reactive oxygen species (ROS) has been a subject of theoretical and practical dispute as experimental designs able to quantitatively evaluate ROS formation. Under normoxic conditions, ROS (constantly generated in erythrocytes) are mostly counteracted by their endogenous (superoxide dismutase, glutathione peroxidase, catalase or reduced glutathione) or exogenous (vitamin C, vitamin E, etc.) antioxidant defense systems. Studies also show that wild-type human hepatoma cells (Hep3B) increase ROS generation of metal-activated cell signaling pathways during hypoxia.^{5,6} Valko M et al.⁷ stated that "hypoxia-activated gene transcription via a mitochondria-dependent signaling process induces increased ROS." The mechanisms by which mammalian cells adapt to acute and chronic alterations of oxygen tension are extremely important to understand the exact homeostasis regulation to counteract hypoxia-induced cell damage as a therapeutic strategy. Heavy metals are capable to induce expression of HIF-1 transcriptional factor and vascular endothelial growth factor (VEGF) genes through the

phosphatidylinositol 3-kinase or Akt pathway or ROS.⁸ Heavy metals-induced alteration of the hypoxia signaling system influenced by metal-induced oxidative stresses are responsible for progression of metastasis. This chapter gives a brief understanding of current state of knowledge of chronic hypoxia and its influence on generation of ROS by inducing oxidative stress in the physiological system. The review will also provide recent update of heavy metal nickel toxicities on oxidant and antioxidant balance and molecular interaction of chronic hypoxia and heavy metal nickel (Ni) in the physiological system in vivo. Cellular hypoxia causes an initiation of hypoxia-response genes responsible for angiogenesis, oxygen transport, and metabolism. 10 Chronic hypoxia stimulates NF-κB gene expressions and it reduces KLF4, which further leads to an enhanced NOS2 expression (Fig. 26.1). Both hypoxia and heavy metal exposure induce generation of ROS and increase expression of p53, NF-kβ, AP-1, MAPK, and HIF-1α. The increase expression of all these transcription factors leads to either cellular adaptation or cell death. 11 It is also to be mentioned that hypoxic injury due to metal assault or hypoxia exposure causes "cell death" by cells swelling, plasma and nuclear membrane disruption, cellular lysis in association with acute inflammation that may exacerbate the initial hypoxic injury response. However, the alternative mode of cell death, apoptosis, is also possible (Fig. 26.1). During apoptosis, the cells use their molecular machinery to shrink or expand into membrane-bound apoptotic bodies, with or without nuclear fragments that are easily phagocytosed by adjacent tissue cells or macrophages and minimize any acute inflammatory response.

Liver is an important metabolically active organ. It stores additional nutrients in the form of glycogen and lipids. During the need of the hour these nutrients yield energy and keep all the vital functions intact. Hepatocytes also synthesize plenty of proteins including albumin and clotting factors. Furthermore, it synthesizes cholesterol and triglycerides. Another important function of liver is to produce bile salts which are essential for digestion and absorption of lipids. The hepatocytes also play an important role as the center of detoxification in the body, influencing drug metabolism and breakdown of hormones. This organ is an important source of storage of vitamins such as B12, A, D, K and folic acid, besides being an important source of iron. To make the liver a well-functioned organ, a considerable amount of oxygen is needed. Altered metabolic functions due to toxic insults or metabolic stress due to hypoxia or heavy metal toxicities disturb oxygen homeostasis in liver and lead to serious liver diseases. Most of the cases, malfunction of liver leads to fatty liver symptoms and the cell signaling pathways greatly affected is oxygen dependent, hence hypoxia may be considered as an important cause of liver malfunction.¹² Interestingly, hypoxia and divalent heavy metals such as nickel (Ni) and lead (Pb) generate ROS and disturbed oxidant/antioxidant balance which is linked to the transcriptional factor HIF- 1α . The results from the author's laboratory showed both divalent cationic heavy metal (Ni and Pb) and chronic sustained hypoxia stimulate the production of HIF- 1α transcription factor and VEGF gene expression in metabolically active tissues in similar molecular mechanism. Heavy metals cause oxidative stress by inducing the generation of ROS; reducing the antioxidant defense system of cells via depleting glutathione; interfering with some essential metal; inhibiting sulfhydryl (SH), dependent enzyme, or antioxidant enzymes activities; and/or increasing susceptibility of cells to oxidative attack by altering membrane integrity and fatty acid composition. 13,14

Nutrients such as vitamin C or E are found to be the most effective circulatory antioxidant in human system. 15 Ascorbic acid or vitamin C prevents lipid peroxidation, oxidation of low-density lipoproteins, and advanced oxidation protein products. 16 Vitamin C may comprise the first line of defense system in RTLF against external pro-oxidative assaults. 17 It has been reported that intracellular depletion of ascorbic acid aggravated some heavy metal (nickel, cobalt, etc.)-induced carcinogenicity and acute toxicity. 18 The effect of simultaneously supplemented vitamin C on experimental nickel treatment

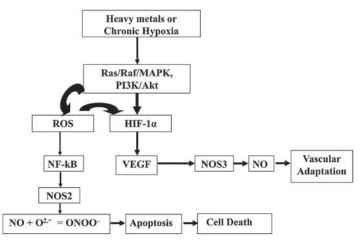


FIGURE 26.1 Graphic representation showing heavy metals or hypoxia-induced common cellular abnormalities. NF- kB, nuclear factor-kappa B; NO, nitric oxide; NOS, nitric oxide synthase; ONOO-, peroxynitrate; HIF-1α, hypoxia inducible factor 1α; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

shows ascorbic acid is capable to reduce intestinal absorption of nickel. The mechanism involves that vitamin C is capable to reduce ferric iron to ferrous iron in the duodenum, thus availability of divalent ferrous ion increases which competes with nickel or lead also as divalent cation for intestinal absorption. 19 Recent reports indicate the capability of ascorbic acid as a regulatory factor may influence gene expression, apoptosis, and other cellular functions of living system exposed to heavy metals.²⁰ This chapter elaborately explains the role of dietary supplementation of nutrients such as vitamins and other nutrients in heavy metals such as nickel and lead, which induces altered hepatic functions in low-oxygen microenvironments.

2. HEAVY METALS AND ITS INTERACTIONS

Heavy metals interact with the biological system in a complex manner. Even elemental speciation of the metals also matters in its interactions with systems. The **term heavy** metal refers to any metallic chemical element that has a relatively high density and is toxic or poisonous at low concentrations. The heavy metals constitute major fraction of the periodic table and are generally interpreted to include those metals from periodic table groups IIA through VIA. Examples of heavy metals are nickel, lead, mercury, cadmium, chromium, etc.¹

2.1 Heavy Metal Toxicities: Nickel and Lead

There are five priority substances which are selected by WHO for the nickel risk assessment. They are nickel powder, nickel sulfate, nickel chloride, nickel carbonate, and nickel nitrate. Nickel powder (T; R48-23) has been classified in chronic toxicity classification as per environmental risk assessment report on nickel. NiSO₄, NiCl₂, NiCO₃, and NiNO₃ are classified as carcinogen class I (by inhalation), reproductive toxicants class II (may cause harm to unborn children), and chronic toxicants (T; R48-23). If particle size of nickel powder found to be less than 0.1 mm, it is classified as T; R52-53 (harmful to the aquatic environment).²¹ Acute toxicity in humans, which results from absorption through the gastrointestinal tract or by inhalation through lungs, was first reported by Sunderman in 1954.²² Further studies showed that a single dose oral LD50 in rats for the less-soluble nickel oxide and subsulfide was >3600 mg Ni/kg bwt, whereas the oral LD50 for the more soluble nickel sulfate and nickel acetate ranged from 39 to 141 mg Ni kg⁻¹ bwt in rats and mice.²³ The metal is not only an allergen but also a potential immunomodulatory and immunotoxic agent in humans. 19 Weischer et al. 24 reported that oral administration of nickel as NiCl2 in male rats over a period of 28 days at concentration of 2.5, 5.0, and 10.0 µg/mL in drinking water (0.38, 0.75, or 1.5 mg/kg day) resulted in significant dose-dependent hyperglycemia, decrease in serum urea, and significant increase in urine urea. At 0.75 mg/kg doses, increased leukocyte count was also observed. It was noticed that exposure of dietary nickel sulfate hexahydrate (100, 1000, or 2500 ppm) to dogs for 2 years failed to produce significant signs of compound-related toxicity. ²⁵ The toxicity of the different nickel compounds is related to its solubility, with soluble nickel sulfate being the most toxic and insoluble nickel oxide being the least toxic. The difference in the toxicity across compounds is probably due to the ability of water-soluble nickel compounds to cross the cell membrane and interact with cytoplasmic proteins.²¹

Lead poisoning can affect almost all parts of the body, but its effects are most pronounced on the central nervous system and kidneys. Lead can impair cognitive development, which can lead to learning disabilities and behavioral problems. Acute lead exposure can cause encephalopathy, severe abdominal pain, vomiting, diarrhea, coma, seizures, and, in some cases, death. Chronic exposure can cause weakness, prolonged abdominal pain, anemia, nausea, weight loss, fatigue, headache, and loss of cognitive function. Chronic, low-level lead exposure can be asymptomatic until kidney function starts to deteriorate.¹¹ Lead has no known physiologically relevant role in the body, and its harmful effects are myriad. Lead and other heavy metals create reactive radicals, which damage cell structures including DNA and cell membranes. Lead also interferes with DNA transcription enzymes that help in the synthesis of vitamin D, and enzymes that maintain the integrity of the cell membrane. Anemia may result when the cell membranes of red blood cells become more fragile as the result of damage to their membranes. Lead interferes with metabolism of bones and teeth and alters the permeability of blood vessels and collagen synthesis. Lead may also be harmful to the developing immune system, causing production of excessive inflammatory proteins; this mechanism may mean that lead exposure is a risk factor for asthma in children. Lead exposure has also been associated with a decrease in activity of immune cells such as polymorphonuclear leukocytes. Lead also interferes with the normal metabolism of calcium in cells and causes it to build up within them. It is metabolized by CYP450 to trimethyl lead (TML). Mechanisms of its toxicity include damage to membranes, disturbances in energy metabolism, and direct interference with neurotransmitter synthesis. Symptoms of its toxicity include nausea, vomiting, diarrhea associated with nervous system problems such as irritability, headache, and restlessness. Chronic heavy sniffing of leaded gasoline results in signs of dementia and encephalopathy, with cerebellar and corticospinal symptoms. Lead primarily acts by competing with endogenous cations on protein-binding sites. In particular, lead can substitute both calcium and zinc in numerous proteins. Among stress-response genes that were upregulated by lead treatment, GFAP, microsomal glutathione S-transferase, mitochondrial 10 KDa heat shock protein, and HSP70 are all involved in general cellular responses to stress. Daphnia hemoglobin gene was greatly expressed following lead exposure.²⁶

3. HYPOXIA PATHOPHYSIOLOGY

Hypoxia is a pathological condition in which the body as a whole (generalized hypoxia) or a region of the body (tissue hypoxia) is deprived of adequate oxygen supply. Variations in arterial oxygen concentrations can be part of the normal physiology, for example, during strenuous physical exercise. In healthy humans, there is a range of physiological oxygen levels within the tissues of the body, ranging from PO2 values of -100 Torr in the alveoli of the lungs to less than 10 Torr in tissues such as the medulla of the kidney and the retina.²⁷

3.1 Hypoxia Microenvironment

Physiological hypoxia is an important microenvironmental signal in a range of processes including new blood vessel formation (angiogenesis) during development and wound healing, the regulation of vascular tone, and the response to exercise. However, tissue hypoxia is also associated with a diverse and wide range of pathophysiological processes including (but not limited to) vascular disease, chronic inflammation, and cancer.² In vascular diseases such as atherosclerosis and stroke, vascular occlusion leads to acute or chronic tissue ischemia with resultant hypoxia. In chronic inflammatory diseases, the greatly increased metabolism of inflamed tissue due to immune cell infiltration matched with vascular dysfunction leads to tissue hypoxia.²⁷ Hypoxia results from conditions such as ischemia, hemorrhage, stroke, premature birth, and other cardiovascular difficulties. Among which hemorrhagic shock is the leading cause of death and complications in combat casualties and civilian settings. It has been shown to cause systemic inflammation response syndrome, multiple organ dysfunctions, and multiple organ failure.²⁸ Hypoxia has been shown to lead to increases in intracellular free calcium concentration (Ca²⁺), 5-lipoxygenase, lipid peroxidation, cycloxygenase (COX), constitutive nitric oxide synthase (cNOS), leukotriene B4 (LTB4), prostaglandin E2 (PGE2), interlukins, tumor necrosis factor- α (TNF- α), caspases, complement activation, kruppel-like factor 6 (KLF6), inducible nitric oxide synthase (iNOS), heat shock protein 70 kDa (HSP-70), and hypoxiainducible factor- 1α (HIF- 1α). The sequence of their occurrence provides the useful information for studying the mechanisms underlying the hypoxia-induced injury as well as therapeutic targets to prevent or ameliorate the injury. Hypoxia, or inadequate oxygenation, causes various responses within the body. Its effects are usually mediated via the activation of HIF-1. HIF-1 activation can lead to upregulation of various genes such as erythropoietin and growth factors that help tissues adjust to the decreasing oxygen availability. Semenza and Wang defined a binding site critical for the hypoxia-inducible function, which involves a transcription factor induced by hypoxia. Subsequently, they purified a DNA-binding complex bound to the HRE by affinity purification using oligonucleotide with the HRE sequence and thus identified the encoding cDNAs.²⁹

3.2 Hypoxia and Heavy Metals (Nickel and Lead)

Over the recent years, induction of signaling pathways that regulate key cellular responses related to cancer growth and progression by metals has been the focus of many studies. The unraveling of these pathways and the deciphering of their interplay with metals should allow a better understanding of metal toxicity and hopefully will enable development of prophylactic strategies and therapeutic approaches. Authors' laboratory and works of Leonard (2004) have shown the mechanisms of toxicities caused by heavy metals such as nickel and lead, emphasizing on the involvement of the hypoxia signaling pathway by metal-induced generation of ROS and oxidative stress generation.^{20,30} Hypoxia-induced factor HIF-1 controls precise oxygen homeostasis by modulating expression of several cancer-related genes, including heme oxygenase 1 and vascular endothelial growth factor. The carcinogenic metals such as nickel, lead (Pb), or chromium have been known to activate HIF-1.8,31 It has been observed that heavy metal-induced ROS generation during the exposure of cells to metals mimic hypoxia-like symptoms.³² The mechanisms of carcinogenesis caused by heavy metals such as nickel emphasizes on the involvement of the hypoxia signaling pathway by metal-induced generation of ROS and oxidative stress generation in cancer progression. One of the pathways by which heavy metals such as nickel and lead induce intracellular hypoxia is by reducing heme biosynthesis. Low level of heme reduces intracellular oxygen tension and simply intracellular low Fe²⁺ and low oxygen tension inhibit PHD₂ (prolyl hydroxylases). Under normoxic conditions, HIF-1-prolyl hydroxylases (PHD) hydroxylate the prolyl residues at amino acids 402 and 564. These enzymes require dioxygen, Fe²⁺, ascorbate, and two oxoglutarates for activity. The hydroxylated peptides interact with an E3 ubiquitin-protein ligase complex composed of pVHL (von Hippel-Lindau tumor suppressor protein), elongin B and C, and Cullin 2 (CUL2), and then poly-ubiquitinized, resulting in HIF-1 α degradation by the 26S proteasome. Under hypoxic conditions, HIF-1 α is not hydroxylated because the major substrate, dioxygen, is not available. The unmodified protein escapes the VHL-binding, ubiquitination, and degradation, and then dimerizes HIF-1 α and stimulates the transcription of its target genes.³³

4. HEAVY METALS IN LIVER DISEASES

Heavy metals related to cardiovascular and pulmonary disorders are quite common and reported elsewhere, but currently, heavy metals and its impact on liver disease are considered as serious as before.³⁴

4.1 Heavy Metals and Liver Pathophysiology (Nickel and Lead)

Fatty liver disease is considered as one of the important causes of chronic liver disease, and it is manifested by a complicated etiology. Heavy metal-induced changes in liver pathophysiology including fatty liver changes are under non-alcoholic fatty liver disease (NAFLD) category. Fatty liver induces a prolonged inflammatory response which leads to fat accumulation in the liver due to hepatocellular damages. One study showed that heavy metals caused NAFLD in men under 24 BMI. In case of overweight and obese, it becomes more serious. It was also observed that lead (Pb) causes more liver damage than nickel (Ni).³⁵ Heavy metals such as nickel and lead cause hepatocellular hyperplasia, which may lead to even carcinoma of liver. Studies on nickel clearly showed elevation of liver aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltranspeptidase. 6,36 Furthermore, it has been found that at advanced stages of hepatic cirrhosis, there was a significant increase of hepatic levels of nickel.³⁷ Another study also showed lower serum nickel concentration in liver cirrhosis patients which attributes a possible reduction of hepatic synthesis of nickel transport protein, i.e., nickeloplasmin and albumin.³⁸ Similarly, study also showed that lead and mercury are linked with NAFLD.³⁹ Furthermore, it was observed that lead (Pb) become conjugated in liver and stored there in highest concentration. Lead exposure on experimental animal showed an elevation of AST, ALT, and alkaline phsophatase, which clearly indicate a possible liver failure.⁴⁰ The most common pathways for metal-induced hepatotoxicity is through free radicals due to oxidative stress. The free radicals which are generated due to heavy metal exposure damage cell membrane lipid bilayers, nucleic acids, and enzymes. These in turn causes functional impairment of cell integrity and disturbs cytoprotective systems. Furthermore, it imparts oxidant and antioxidant imbalances and leads to cellular injuries. The mechanisms of hepatotoxicities are through affecting hepatic mitochondrial respiratory systems by reducing cytochrome c oxidase activity. Excessive accumulation of heavy metals also disturb hepatic calcium regulatory system by damaging microsomal calcium sequestration and damaging hepatocellular DNA, which further leads to carcinoma of liver.⁴¹

4.1.1 Nickel and Hepatotoxicities

A transient increase in serum bilirubin was observed in 3 out of 10 workers who were hospitalized after drinking water from a water fountain, contaminated with nickel sulfate. 41 In rats, decreased liver weight was observed following exposure for 28 days to 2 year to 0.97–75 mg/kg day of nickel chloride or nickel sulfate. 42 Recent studies on rats by Das et al. 43 revealed a nickel sulfate-induced degenerative effect on hepatic tissue They have observed that after the intraperitoneal injection of nickel sulfate, normal hepatic architecture was greatly altered, along with appearance of vacuolated cytoplasm (fatty liver), eccentric nuclei, and Kupffer cell hypertrophy. One report described decreased hepatic and renal transaminase activities after nickel treatment in rats, which was found more deleterious in a protein-restricted dietary regimen.⁴⁴ Nickel sulfate also decreases the liver ascorbic acid and cholesterol levels in rats. 6 Misra and coworkers showed that a single intraperitoneal injection of nickel (II) acetate increased lipid peroxidation and glutathione-S-transferase activity in rat liver and kidney while concomitantly decreasing the glutathione concentration and glutathione reductase activity. 45 The same group found that the nickel-induced hepatic lipid peroxidation in different strains of mice was concurrent with nickel's effect on antioxidant defense systems in liver and kidney.⁴⁶ The magnitude of nickel-induced lipid peroxidation showed a reverse correlation with the extent and direction of its effect on glutathione and glutathione peroxidase glutathione reductase but not on CAT, SOD, or glutathione-S-transferase.⁴⁶ Das et al.⁴⁷ showed, after the nickel treatment of rats, a significant rise in hepatic lipid peroxides and a decrease in antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities and in the hepatic glutathione concentration. The alteration of oxidant and antioxidant balance due to hepatic lipid peroxidation indicates an elevation of enzyme phospholipase activities while peroxidic disintegration of various subcellular organelles and membrane lipid layers with nickel exposure. Furthermore, it may be postulated that nickel causes Kupffer cell hyperactivity through inflammatory cytotoxic mediators along with fatty liver changes and

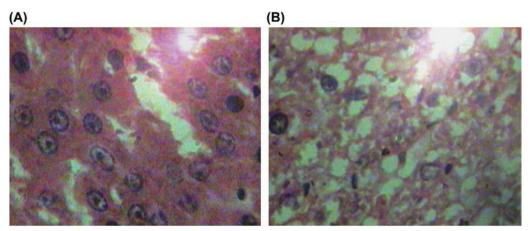


FIGURE 26.2 Normal (A) and nickel sulfate (B)-treated rat liver histopathology (45×).

eccentric nuclei in hepatocellular architecture. Nickel-induced changes of hepatic SOD, CAT, and GSH-Px reveal possible interaction of free radicals and hepatic enzymes and damaging SH protective mechanism against lipid peroxidation.⁴⁷ Study also revealed that nickel or some other heavy metals cause alteration in hepatic HMG-CoA reductase activities and disturb LDL-receptor gene expression. It ultimately changes the lipid profile of physiological system. 48,49 Another study showed that nickel induced severe liver damage as indicated by rise of SGOT, SGPT, and ascorbate-cholesterol metabolism in experimental rats. The study also showed that nickel sulfate causes decrease in absolute liver weight without altering hepatosomatic index which is indicative of hepatic degenerative changes.⁵⁰ Increased activity of SGOT and SGOT after nickel exposure reflects possible leakage of hepatic enzymes from liver cytosol in circulatory system due to nickel-induced cellular damages.⁵¹ Another observation on nickel-induced hyperglycemia in experimental animals indicates a marked reduction in hepatic fructose-2-6-bisphosphate, which is an indicator of gluconeogenic and glycolytic pathways suggestive of increase of liver gluconeogenesis.⁵²

In histopathological studies in the author's laboratory, the liver showed congestion of central veins and sinusoids and some hepatocytes suffered from vacuolar degeneration, fatty changes, etc. (Fig. 26.2A and B). Mathur et al. also observed the same in nickel sulfate-treated rats.⁵³ Results from the author's laboratory are in agreement with those obtained by El-Saeed and Mekawy⁵⁴, Ptashynski and Klaverkamp,⁵⁵ and Sobecka⁵⁶. Nickel intoxication causes a vacuolization of the cytoplasm, the increase in numbers of pyknotic nuclei, and the decrease in glycogen content in hepatocytes.⁵⁷ The hydropic degeneration of hepatocytes may be due to the irritation of toxic metabolites and impairment of potassium sodium pump that disturbs the ion exchange through the cell wall. The increased oxidative stress, the formation of ROS as well as depletion of cellular antioxidant level may be resulted in histopathological changes of liver. Heavy metal-induced interstitial fibrosis, increased numbers of pyknotic nuclei, as well as necrosis in hepatocytes have also been reported earlier.⁵⁸

4.1.2 Lead and Hepatotoxicities

Like nickel, lead too raises serum LDL-cholesterol, VLDL-cholesterol, total cholesterol and triglycerides, and decreases serum HDL-cholesterol and HDL/LDL ratio. It may be due to changes of the gene expression of hepatic enzymes and LDL receptor synthesis. Defects in the LDL-receptor interfere with cholesterol uptake from the bloodstream, which in turn causes excess cholesterol synthesis in the liver and high levels of serum total cholesterol and LDL-cholesterol.⁴⁸ The improvement of serum lipid profile also reflects normalization of liver P450 enzyme system function by α -tocopherol.⁵⁹ Lead generates long-lived ROS. These might cause oxidative stress that results in oxidative deterioration of biological macromolecules leading to oxidative damage to the hepatic cells.⁶⁰ In an experimental study, lead acetate induced increase plasma MDA with decreased hepatic SOD, CAR, and GSH-Px were noticed which are indicative of hepatic oxidative stress.⁶¹ During hepatotoxicity, these enzymes are structurally and functionally impaired by free radicals, resulting in liver damage. Glutathione comprises up to 90% of the nonprotein thiol content of mammalian cells and performs a pivotal role in maintaining their metabolic and transport functions. It acts as a nucleophilitic "scavenger" of many compounds and their metabolites via enzymatic and chemical mechanisms, converting electrophilic centers to ether bonds. Glutathione depletion to about 20%-30% of total glutathione levels can impair cell defenses against toxic actions, which may lead to cell injury

FIGURE 26.3 Normal (A) and lead acetate—(B) treated rat liver histopathology (45x).

and death.²¹ Furthermore, glutathione is considered a crucial factor in maintaining the structural integrity of cell membranes, largely through reactions that protect the membrane against free radical formation.⁶² Lead interacts with negatively charged phospholipids in membranes and through the induction of changes in membrane physical properties could facilitate the propagation of lipid oxidation in liver. Lead affects membrane-related processes such as the activity of membrane enzymes, endo- and exocytosis, transport of solutes across the bilayer, and signal transduction processes in hepatocytes by causing lateral phase separation.^{30,61} Lead-induced oxidative stress in liver caused increase of rate of production of hydroxyl radicals which may lead to lysosomal and mitochondrial damages. Besides these direct hepatocellular damaging by lead-induced ROS and reactive nitrogen species (RNS), it may also interfere cell signal transduction by reversible oxidation and nitrosation of protein SHs in the hepatic sinusoid.⁶³

Histopathological studies of lead-treated rat liver from the author's laboratory indicated little swollen hepatocytes with ill-defined cell borders with variation in cellular size and shape. The nuclei are large, more vesicular with variable size and shape, and contain multiple three to four prominent nucleoli. The cytoplasm is vacuolated and microvesicular. There are foci of fatty change and ballooning degeneration and necrosis of hepatocytes in zone 3 (centrilobular) areas.

The portal area appears mildly enlarged with mild proliferation fibrous tissue with infiltration of mixed acute and chronic inflammatory cells. The sinusoidal spaces are variably widened with increase in number of Kupffer cells. Central vein shows features of dilatation and congestion (Fig. 26.3B). Results clearly indicate hepatocellular damage by lead exposure.

4.2 Possible Mechanism of Altered Hepatocellular Architecture by Heavy Metals

It was found that most of the divalent heavy metals such as nickel, lead, and cadmium enter into systemic circulation from intestine through metal transporter proteins (MTP 1). Through circulation these metals enter first to liver via portal circulation where it is absorbed through sinusoidal capillaries. In hepatocytes, these heavy metals are penetrated through specific membrane transporters such as DMT1, ZIP8, and ZIP14t.^{64,65}

Heavy metals such as nickel or lead accumulate in liver and resulting hepatocellular damages induce infiltration of polymorphonuclear neutrophils. This in turn causes activation of Kupffer cells followed by necrosis. Usually heavy metal-activated Kupffer cells secretes several inflammatory cytokines and causes secondary liver damage. 66 The exact mechanism of hepatocellular damages by Kupffer cells is yet to be cleared, but a possible role of free radicals, nitric oxide, tumor necrosis factor α (TNF-α) cannot be ruled out⁶⁷ (Fig. 26.4). Studies on nickel showed hepatic apoptosis due to overexpressions of caspase-3, caspase-9, and PARP mRNA.⁶⁸

5. HYPOXIA AND LIVER DISEASES

Liver pathophysiology is oxygen dependent. As it is an important organ for metabolism, it is always in demand for oxygen. Hepatic artery, portal veins, and central veins play the pivotal role to maintain liver oxygen homeostasis.⁶⁹ It was found that liver always make oxygen microenvironment differentially than other organs. The important change

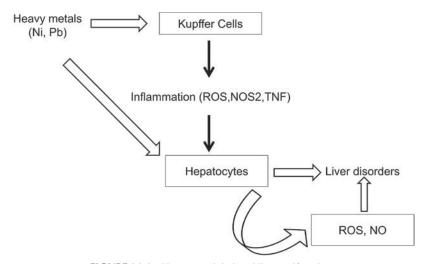


FIGURE 26.4 Heavy metal-induced liver malfunctions.

in hypoxia-induced hepatocellular architecture is the formation of plasma membrane protrusion. This formation has numerous cytosol and endoplasmic reticulum. It ultimately causes swelling of mitochondria and near 30%–50% increase of cell volume. These changes can be reversed if reoxygenation to hepatocytes occurs. The hepatocytes may be permanently injured if hypoxia sustains, and it will lead to complete damage of plasma membrane transport system which will cause release of intracellular ingredients of hepatocytes. 70 Oxygen tension in periportal and perivenous part of liver is 60-75 mmHg and 30-35 mmHg, respectively, which clearly indicates a persistent hypoxia in liver due to high metabolic functions.⁶⁹ Study reveals that hypoxia is linked to several types of liver diseases. The mechanism by which hypoxia is able to change liver pathophysiology is mainly through HIF-1 and NOS2 expressions. Both these factors are involved in hepatocytes, Kupffer cells, and immune cells. Hypoxia in liver increases the level of TNF-α, IL-1 from hepatocytes which further promote ROS. These ROS in liver are found to have decreased glutathione levels and elevated oxidized glutathione.⁷¹ Although a direct hypoxia response to liver was not found in healthy individuals, in the case of viral hepatitis, metabolic diseases, steatohepatitis, and cancer, an elevation of HIFs is noticed. It has been observed that HIFs induce pathogenesis of hepatocellular carcinoma, and both HIF-1 α and VEGF levels were increased in hepatocellular carcinoma.⁷² Many chronic liver diseases due to vital infection, metabolic disorders, or alcoholism are found to be connected with HIFs.⁷³ Actually HIFs act as protective agents from liver injuries due to hypoxia. HIFs induce generation of VEGF, adenosine, nitric oxide, and Akt signaling pathways to prevent hepatocellular injuries from hypoxia.^{74,75} It is observed that Dec1 expression increases in alcoholic liver which indicates HIF-1α regulatory gene involvements to protect liver of alcohol toxicities. Hypoxia region of liver shows alteration of parenchymal vasculature, which leads to fibrosis. ⁷⁶ HIF-1α expression stimulates hepatic stellate cells (HSCs) and fibroblasts. Another study on NAFLD phenotype showed hypoxia accelerated the NAFLD phenotype with higher level of lipogenesis and inflammation.⁷⁷ Another important phenomenon of hypoxia-induced liver injury is through ATP depletion during hepatic ischemia which also leads to necrotic cell death. Hypoxic liver enhances glycolytic metabolism and prevents its best against hypoxia injuries. In case of low glycogen in liver, hypoxia leads to rapid cellular ATP depletion and necrosis.⁷⁸ Hypoxia-exposed liver also shows alteration of pH microenvironment. Hypoxia leads to acidosis in liver, which prevents necrotic cell death in liver in spite of low ATP levels.⁷⁹

5.1 Hypoxia—Liver Histopathology

In histopathological studies in the author's laboratory, the subchronic hypoxia-exposed rat liver showed endothelial cells surrounded by a ring of collagen fibers in the central vein. The sinusoids are lined by both endothelial cells and Kupffer cells both of which have inconspicuous flattened nuclei and ill-defined cytoplasmic margins. The hepatocytes are polygonal in shape with well-defined borders and appear to be little swollen with mild narrowing of the sinusoidal spaces. The nucleus is single, is round, and has a fine chromatin pattern with one to two clearly defined amphophilic prominent nucleoli. More or less it reflects normal architecture with insignificant changes in hypoxia-exposed rat liver (Fig. 26.5B).

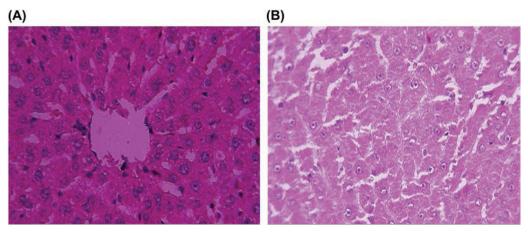


FIGURE 26.5 Normal (A) and chronic hypoxia- (B) exposed rat liver histopathology (45×).

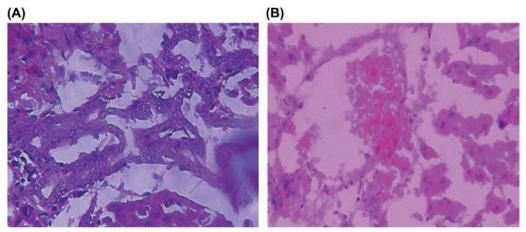


FIGURE 26.6 Hypoxia exposed with nickel sulfate—(A) and lead acetate—(B) treated rat liver histopathology (45×).

5.2 Hypoxia and Heavy Metals (Nickel and Lead)—Liver Histopathology

There is evidence of fatty change and ballooning degeneration and necrosis of hepatocytes. The portal area appears enlarged with severe proliferation fibrous tissue with infiltration of mixed acute and chronic inflammatory cells in nickel sulfatetreated subchronic hypoxia-exposed rats (Fig. 26.6A). In the case of subchronic hypoxia-exposed lead acetate-treated rats, distorted "lobular" architecture of liver parenchyma is noticed. Hepatocytes appear to be little swollen and cytoplasm is vacuolated, microvesicular, and eosinophilic (Fig. 26.6B). It also shows increase in number of mitotic figures along with foci of fatty change and ballooning degeneration and necrosis of hepatocytes in zone 3 (centrilobular) areas. Moderate proliferation of a portal area with fibrous tissue with infiltration of mixed acute and chronic inflammatory cells and variable widening of sinusoidal spaces along with Kupffer cell hyperplasia, dilatation, and congestion of central vein are also observed.

6. HEAVY METALS (NICKEL AND LEAD), HYPOXIA, AND LIVER FUNCTIONS—ROLE OF **DIETARY SUPPLEMENTATIONS**

Dietary supplementation of protein and other antioxidants including chelators are found to be effective against metal-induced hepatotoxicities. It has been found that metal ions interact with protein in a coordinated manner and chelate. These protein chelator compounds change the toxic characteristics of heavy metals by degrading it. The mode of hepatotoxicities by toxic metals such as nickel and lead are similar with hypoxia exposure. The cell signal pathways of nickel or lead and hypoxia usually take place through HIF-1α expressions and further manifestation of expression of hepatic VEGF and NOS2. Both nickel or lead and hypoxia exposure induce ROS and inflammatory cytokines and damages hepatocytes, and interestingly, dietary supplementation of antioxidants such as vitamins C or E and high proteins combat the toxicities from these exposures.

6.1 Heavy Metals, Liver Functions, and Dietary Supplementation

The most common therapeutic way to combat heavy metal toxicity is chelation therapy which leads to metal excretion, but chelators themselves have many contraindications. Chelators such as EDTA and meso-2,3-dimercaptosuccinic acid (DMSA) are routinely used against Pb poisoning, but no such chelators are found to detoxify nickel poisoning so far. Hence alternative therapy, especially dietary supplementation, is now gaining momentum against heavy metal poisoning. As per WHO and the US Dietary Supplements Health and Education Act (DSHEA) of 1994, vitamins, minerals, herbs, amino acids, or other food substances additionally supplemented in diets are considered as dietary supplementation.⁸⁰ Most of the cases these dietary supplementations are found to be safe for health.⁸¹ Some studies showed that Zn or Se are protective against Pb and Ni toxicity in liver, kidney, and brain. These micronutrients facilitate antioxidant defense mechanisms of metabolically active tissues including liver by acting as cofactor for synthesis of glutathione peroxidase (GSH-Px).82 One interesting observation is the beneficial role of iron supplementation in metal exposure. In presence of dietary supplemented iron, it competes with other divalent cations derived from metals such as Ni, Cd, or lead at the level of its transporter proteins such as divalent metal transporter-1 (DMT1) and metal transporter protein 1 (MTP1) in the intestine and reduced uptake of these heavy metals.⁸³ Dietary supplementations of some elements such as calcium or magnesium are also found to be effective against Pb or Ni toxicity. The elements usually decreases heavy metal absorption from intestine or competitively binds with active sites of intracellular metal-binding protein in hepatic tissues and prevent heavy metals such as nickel, cadmium, and lead to exert hepatic tissue damages. 84,85 Some dietary supplementations such as Allium sativum Linn (garlic) were found to be hepatoprotective against heavy metals such as nickel and chromium VI.86 Garlic has been found to be effective against heavy metal toxicities in liver through a number of mechanisms, such as scavenging radicals, increasing glutathione levels, increasing the activities of enzymes such as glutathione S-transferase and catalase, and inhibiting cytochrome p4502E1. Studies of Vimal and Devaki⁸⁷ showed that allicin (diallyl thiosulfinate) which is the main biological active compound derived from crushed garlic is highly protective against Cr VI- or lead-induced hepatic lipid peroxidation. Garlic also contains a number of amino acids that are required for the formation of an enzymatic antidote to free radical pathology, which is created by various pollutants including heavy metals. Cysteine, glutamine, isoleucine, and methionine found in garlic help to protect the liver cells from such free radical damage.^{88,89} Raw garlic extract can effectively protect the body from metal toxicity. Garlic contains the highest level of the antioxidant selenium, which affords excellent hepatocellular protection.⁸⁹ Vitamin supplementations in diet are extremely popular against heavy metal toxicities as low concentration of vitamins C, B1 and B6 are found to have increased sensitivity toward Cd, Ni, and Pb toxicity in hepatic tissues. 90 It is further observed that vitamins C and E are natural exogenous nonenzymatic antioxidants which prevent liver from oxidative stress by preventing hepatic lipid peroxidation. 47 Besides antioxidant actions, vitamin C also acts as a chelating agent like EDTA against Pb toxicities in hepatic tissues. 91 Experimental study in rats has shown a beneficial effect of vitamin E pretreatment against heavy metals induced an alteration in liver antioxidant defense mechanisms.^{20,92} Supplementation of vitamins B1 and B6 were found to be effective in decreasing Pb concentration in liver by reversing ALAD activity. Vitamin B1 facilitates Pb excretion and reduces the Pb toxicity.⁹³ Other good hepatoprotective agents against heavy metal toxicity are black tea or green tea, grapes, and tomatoes. The bioactive constituent of these edibles are mainly catechins, flavonoids, and polyphenols. These compounds are antioxidants by nature and act as chelators against Pb-, Ni-, or Cd-induced hepatotoxicity. 94-96 Some other plants such as liquorice (Glycyrrhizae radix) and ginseng (Panax ginseng Meyer) are also found to be effective against Cd-, nickel-, and Pb-induced hepatotoxicities. These plants are routinely used in diet by Chinese, Malaysians, and Africans. 97,98 Currently, some probiotics such as Lactobacillus rhamnosus, L. plantarum, and Bifidobacterium longum are found to be effectively neutralizing heavy metals in vitro. Besides this, these probiotics also act as antioxidants. Probiotic such as L. plantarum CCFM8610 is capable to reduce intestinal absorption of heavy metals and reduces metals deposition in liver and reversing hepatocellular damages due to heavy metal toxicities. 99,100 Another dietary option against heavy metal-induced hepatotoxicity is use of algae as it contains good amount of vitamin C, vitamin E, carotene, etc. which help to reduce heavy metal-induced oxidative stress.¹⁰¹ High dietary supplementation of protein was also found to be effective in liver metabolism against nickel-induced toxicities.⁶

6.2 Hypoxia, Liver Function, and Dietary Supplementation

It has been found that supplementation of vitamins C and E on hypoxic rats improves hepatic glutathione level as compared with only hypoxia-exposed rats. It may be due to antioxidant vitamins C and E protect thiol status in the liver from hypoxia

injuries.²⁰ Antioxidant vitamins such as vitamins C and E also protect hepatocellular reduction of GSH-Px due to hypoxia exposure by decreasing phospholipid hydroperoxides in the cell membrane and prevent further lipid peroxidation.²⁰ These two antioxidant vitamins usually conjugate with GSH-Px and are able to decrease phospholipid hydroperoxide in liver to inhibit lipid peroxidation. 102 Results show that vitamin C and vitamin E are oxidized by ROS and RNS generated by hypoxia exposure in liver tissues. During combating with these TOS and RNS, tissue produce superoxide, hydroxyl, peroxyl, and nitroxide radicals, as well as nonradical reactive species such as singlet oxygen, peroxynitrite, and hypochlorate. These scavenging actions truly prevent lipid peroxidation, DNA and protein damage in liver. These antioxidants further enter into mitochondria and guard it from oxidative stress-induced damages. It must be noted that mitochondria of living cells including hepatocytes generate lots of intracellular ROS, and vitamins C and E supplementation defend mitochondrial genome. 103 Study shows that hypoxia exposure leads to decrease of hepatic concentration of vitamin C which may be due to overutilization of vitamin C by the liver tissues to counteract altered oxygen microenvironment in liver.¹¹ It was noticed that supplementation of vitamin E modifies altered oxygen-sensitive VEGF protein expression in hepatic tissues of hypoxic rats which may be through NOS2. In addition to direct cellular oxidant injury by hypoxia exposure, ROS and RNS may constitute signals regulating by either protein function through reversible oxidation and/or nitrosation of protein SHs or gene expression, in the hepatic sinusoid. Normally nitric oxide (NO) is synthesized by NOS2 gene expression and produced RNS in liver due to hypoxia-exposed low-oxygen microenvironment. Such low-oxygen microenvironment in hepatocytes, Kupffer cells, and endothelial cells generate redox-sensitive transcription factor NF-KB. 104 Study also revealed that the hepatoprotective effect of vitamins C and E under conditions of hypoxia appears to be due to its influence on the functional activity of adrenal glands. It was reported that these antioxidant vitamins enhanced noradrenaline-mediated activity in hypoxia through an iodoacetic acid-sensitive pathway. 105

6.3 Heavy Metals, Hypoxia, and Liver Functions—Dietary Supplementation

Heavy metals such as nickel or lead and hypoxia exposure in liver tissues damage its integrity and develop hepatic malfunctions through ROS and RNS regulatory system. Interestingly, the toxic manifestation for both heavy metals and hypoxia in hepatic tissues are common by nature, i.e. increasing production of ROS and RNS subsequently increase expression of HIF-1 α. It was found that HIF-1α which expresses in tissue exposed to hypoxia as adaptive mechanism is important to regulate metabolism in liver and kidney. 106 Furthermore, it is noticed that HIF-1 plays an important role to develop fatty liver and hepatic fibrosis. It is also noticed that hypoxic area in fibrotic liver due to heavy metals or chronic hypoxia exposure localized with VEGF expression in hepatocytes and HSCs. 107

The possible mechanism by which vitamins C and E counteract HIF-1α transcription factor expression may be through regulating/inhibiting ROS formation and indirectly controlling over production of RNS. Hypoxia- and heavy metal treatment-induced HIF-1α gene transcription actually facilitate VEGF gene expression in hepatocytes to improve adaptability against chronic sustained hypoxia and metal-induced cellular hypoxia in physiological system. 108 Reports suggested existence of a feedback mechanism between ROS production and HIF-1 α in metabolically active tissues, although this link is a complex phenomenon which involves oxidative phosphorelation in response to hypoxia or heavy metals.¹⁰⁹ Furthermore, it is noticed that oxidative phsophorylation in metabolic tissues modulate not only ROS but also oxygen redistribution and consumption by interfering HIF- 1α degradation pathways and over expression of endogenous antioxidant enzymes. 110

6.3.1 Heavy Metals, Hypoxia, Vitamin C and E Supplementation—Liver Histopathology

The author's laboratory shows histopathological changes in nickel- and lead-treated rat liver with or without supplementation of vitamin C and E (Fig. 26.7A–G).

Fig. 26.7C and D shows the effect of vitamins C and E supplementation on nickel-treated rat liver histopathology. It shows that the hepatic parenchymal tissue architecture is maintained normal, which is composed of numerous hexagonal to pyramidal "lobules." Each lobule consists of a central vein from which the hepatic plates radiate outward toward the portal areas; three to five portal triads are located at the periphery of the lobule containing branches of bile duct, portal vein, and hepatic artery; and occasional mononuclear cells. Cords of hepatocytes and blood-containing sinusoids radiate from central vein to the peripheral portal triads. The hepatocytes are large having well-defined cell borders with mild variation in cellular size and shape. The nuclei are round, regular, and vesicular with one to two prominent nucleoli. The cytoplasm is eosinophilic and hypergranular. The portal area appears mildly enlarged with mild proliferation fibrous tissue. The sinusoidal space appears normal with moderate number of Kupffer cells. Central vein shows features of mild dilatation and congestion. No foci of fatty change/hyaline change/degeneration/necrosis/inflammatory reaction are found in vitamins

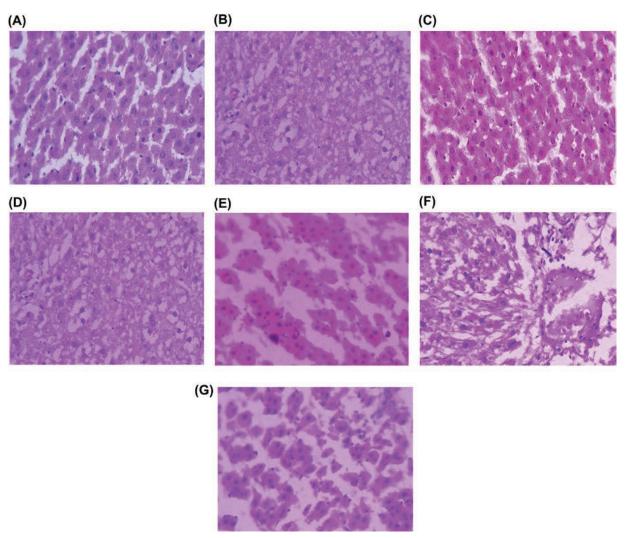


FIGURE 26.7 Normal (A), nickel sulfate—(B), nickel sulfate with vitamin C-(C), nickel sulfate with vitamin E-(D), lead acetate—(E), lead acetate with vitamin C-(F), and lead acetate with vitamin E-(G) treated rat liver histopathology (45x).

C and E supplemented nickel-exposed rats. Results clearly indicate an improvement of hepatic architecture in nickel- or lead-exposed rats supplemented with either vitamin C or vitamin E. Fig. 26.7F shows hepatic parenchymal tissue with mild distortion of "lobular" architecture which is consisting of a central vein, hepatic plates, and portal areas containing branches of bile duct, portal vein, and hepatic artery in vitamin C-supplemented lead treated rat. The hepatocytes are large having ill-defined cell borders with mild variation in cellular size and shape. The nuclei are round, regular, and vesicular with one to two prominent nucleoli. The cytoplasm is vacuolated to clear type with decreasing eosinophilia containing micro/macro vesiculations. There are mild foci of fatty change and ballooning degeneration and necrosis of hepatocytes in zone 3 (centrilobular) areas. The portal area appears mildly enlarged with mild proliferation fibrous tissue with infiltration of mixed acute and chronic inflammatory cells. The sinusoidal spaces are variably widened with pronounced increase in number of Kupffer cells. Central vein shows features of dilatation and congestion. Fig. 26.7G shows near normal architecture of liver parenchyma. Hepatocytes appear normal with sinusoidal spaces that appear normal with moderate number of Kupffer cells. Cytoplasm is eosinophilic and central vein appears normal. Results indicate vitamin E is a better protector than vitamin C against lead-induced hepatotoxicities.

The study on experimental rats in the author's laboratory shows the liver histopathology in hypoxia-exposed and vitamins C and E-supplemented hypoxia-exposed rats (Fig. 26.8A-D).

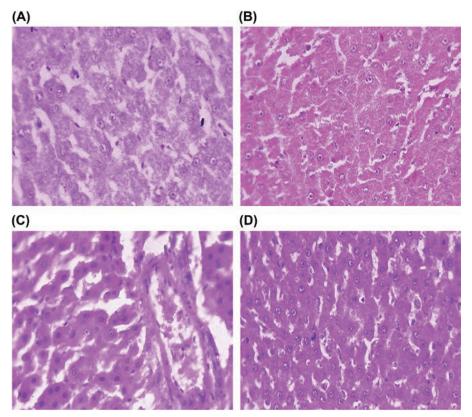


FIGURE 26.8 Normal (A), hypoxia exposed (B), hypoxia exposed with vitamin C-(C), and hypoxia exposed with vitamin E-supplemented rat liver histopathology (45x).

Fig. 26.8B shows hypoxic liver architecture. The central veins are lined by endothelial cells surrounded by a ring of collagen fibers. The sinusoids are lined by both endothelial cells and Kupffer cells both of which have inconspicuous flattened nuclei and ill-defined cytoplasmic margins. The hepatocytes are polygonal in shape with well-defined borders and appear to be little swollen with mild narrowing of the sinusoidal spaces. Microscopic profile shows normal architecture of liver parenchyma maintained with mild narrowing of the sinusoidal spaces. Cytoplasm is more eosinophilic and hypergranular. Fig. 26.8C showed vitamin C shows normal architecture of liver parenchyma is maintained. Mild narrowing of the sinusoidal spaces with portal triad shows mild proliferation with mild thickening of basement membrane of the blood vessels. No obvious significant changes are noticed. In the case of vitamin E-supplemented hypoxic rat liver, normal architecture of liver parenchyma is maintained but hepatocytes appear to be little swollen with mild narrowing of the sinusoidal spaces. The nucleus is single, is round, and has a fine chromatin pattern with zone 1 to 2 clearly defined amphophilic-prominent nucleoli (Fig. 26.8D). Fig. 26.9A shows effect of vitamin C supplementation on hypoxia-exposed nickel (Ni)-treated rat liver. The experimental studies from the author's laboratory on histopathology of liver clearly indicate near normal architecture of liver parenchyma. Hepatocytes appear normal, and sinusoidal spaces appear also normal with moderate number of Kupffer cells. Cytoplasm is appeared to be eosinophilic. Histopathology also indicates normal central vein with normal portal triad. Results show beneficial effect of vitamin C on nickel-treated hypoxic rat liver as compared with rats without vitamin C supplementation (Fig. 26.6A). In case of vitamin E supplementation on nickel-treated hypoxic rats, mild distortion of "lobular" architecture of liver parenchyma and large hepatocytes with mild variation in cellular size and shape are observed (Fig. 26.9B). Furthermore, liver histopathology reveals that cytoplasm is vacuolated to clear type with decreasing eosinophilia containing micro- and macrovesiculations. There are foci of fatty change and ballooning degeneration and necrosis of hepatocytes in zone 3 (centrilobular) areas and mild proliferation of portal area with fibrous tissue with infiltration of mixed acute and chronic inflammatory cells. Variable widening of sinusoidal spaces are also seen (Fig. 26.9B). Although results indicate a relative beneficial effect of vitamin E supplementation on nickel-treated hypoxic rat liver when compared with nickel-exposed hypoxic rats (Fig. 26.6A), it looked relatively less beneficial when compared with vitamin C-supplemented nickel-treated hypoxic rats (Fig. 26.9A).

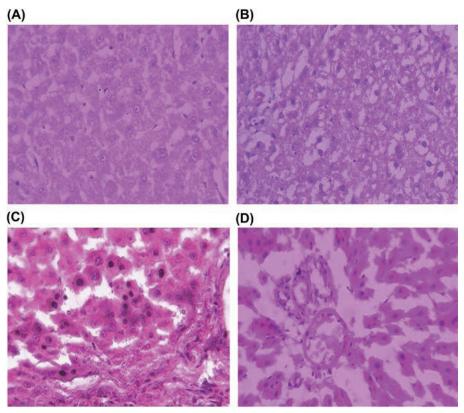


FIGURE 26.9 Nickel and hypoxia exposed vitamin C- (A) and vitamin E- (B) supplemented; lead and hypoxia exposed vitamin C- (C) and vitamin E- (D) supplemented rat liver histopathology (45×).

In authors' laboratory, liver histopathology of lead (Pb)-treated hypoxic rats supplemented with vitamins C and E was also done. Results show a normal architecture of liver parenchyma with mild swollen hepatocytes. Mild narrowing of the sinusoidal spaces was also observed. Portal triad shows mild proliferation with mild thickening of basement membrane of the blood vessels. There were no foci of fatty change or necrosis or inflammatory reaction in histopathology of liver observed (Fig. 26.9C). Fig. 26.9D shows the liver histopathology of Pb-treated hypoxic rats supplemented with vitamin E. Mild distortion of "lobular" architecture of liver parenchyma and vacuolated cytoplasm with decreasing eosinophilia containing micro-and macrovesiculations is noticed. Furthermore, mild proliferation of portal area with fibrous tissue with infiltration of mixed acute and chronic inflammatory cells is also found. Central vein shows features of dilatation and congestion. Results definitely indicate a relative beneficial role of vitamin E supplementation on liver histopathology in lead (Pb)-treated hypoxic rats as compared with lead-treated hypoxic rats without vitamin E supplementation (Fig. 26.6B).

7. CONCLUSION

It may be postulated that heavy metals such as nickel (Ni) or lead (Pb) cause serious cellular damages including hepatocellular damages. Interestingly, chronic sustained hypoxia also induces hepatotoxicities. The molecular mechanisms involved in both the cases are similar by nature.

Heavy metals such as nickel or lead induce hypoxia over expressions of HIF-1α in hepatocellular environment which will be followed by generation of ROS and further expression of VEGF and NOS2 gene in liver. This overexpression of HIF-1α also alters hepatic glycolytic pathways by changing Glut1, LDH, and PFR genes. All these changes lead to hepatocellular damages (Fig. 26.10). Dietary supplements, especially antioxidants such as vitamins C and E are found to be beneficial as they suppress either metal- or hypoxia-induced hypoxia gene expressions in hepatocytes.

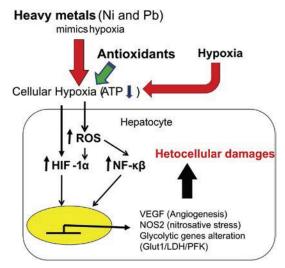


FIGURE 26.10 Heavy metal—and hypoxia-induced molecular mechanisms of hepatotoxicities. Red arrow indicates toxicities and green arrow indicates protection.

ACKNOWLEDGMENTS

The first author greatly acknowledges Life Sciences Research Board, DRDO, Ministry of Defence, Government of India (R&D/81/48222/LSRB-285/EPB/2014 dated 18/7/2014) and VGST, Government of Karnataka (VGST-KFIST/1230/2015-16 Dated 22/6/2016) for providing research grant to him. Author also acknowledges the kind supports of Prof. B.G. Mulimani, former vice chancellor, BLDE University, Vijayapura, India.

REFERENCES

- 1. Das KK, Dasgupta S. Alteration of testicular biochemistry during protein restriction in nickel treated rats. Biol Trace Elem Res 1997;60:243-8.
- 2. Ratcliffe PJ, O'Rourke JF, Maxwell PH, Pugh CW. Oxygen sensing, hypoxia-inducible factor-1 and the regulation of mammalian gene expression. J Exp Biol 1998;201:1153-62.
- 3. Taylor CT. Interdependent roles for hypoxia inducible factor and nuclear factor-kappaB in hypoxic inflammation. J Physiol 2008;586:4055–9.
- 4. Colgan SP, Taylor CT. Hypoxia: an alarm signal during intestinal inflammation. Nat Rev Gastroenterol Hepatol 2010;7:281-7.
- 5. Schumacker PT. Current paradigms in cellular oxygen sensing. Adv Exp Med Biol 2003;543:57–71.
- 6. Das KK, Dasgupta S. Studies on the role of nickel in the metabolism of ascorbic acid and cholesterol in experimental animals. Ind J Physiol Allied Sci 1998:52:58-62.
- 7. Valko M, Morris H, Cronin MTD. Metals, toxicity and oxidative stress. Curr Med Chem 2005;12:1161–208.
- 8. Gao N, Jiang BH, Leonard SS, et al. p38 signaling-mediated hypoxia-inducible factor 1 alpha and vascular endothelial growth factor induction by Cr(VI) in DU145 human prostate carcinoma cells. J Biol Chem 2002;277:45041–8.
- 9. Galanis A, Karapetsas A, Sandaltzopoulos R. Metal-induced carcinogenesis, oxidative stress and hypoxia signaling. Mutat Res Genetic Toxicol Environ Mutagen 2009;674(1-2):31-5.
- 10. Adrian LH. Hypoxia-A key regulatory factor in tumor growth. Nat Rev Cancer 2001;2:38-47.
- 11. Das KK, Saha S. Hypoxia, lead toxicities and oxidative stress: molecular interactions and antioxidant (vitamin C) defense. Curr Signal Transduct Ther 2014:9:113-22.
- 12. Suzuki T, Shinjo S, Arai T, et al. Hypoxia and fatty liver. World J Gastroenterol 2014;20(41):15087–97. https://doi.org/10.3748/wjg.v20.i41.15087.
- 13. Hande G, Nuran E. Can antioxidants be beneficial in the treatment of lead poisoning? Free Radic Biol Med 2000;29(10):927–45.
- 14. Das KK, Gupta AD, Dhundasi SA, et al. Protective role of l-ascorbic acid on antioxidant defense system in erythrocytes of albino rats exposed to nickel sulfate. Biometals 2007;20(2):177-84.
- 15. Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. Proc Natl Acad Sci USA 1989;86:6377-81.
- 16. Frei B. Efficacy of dietary antioxidants to prevent oxidative damage and inhibit chronic disease. J Nutr 2004;134:3196S-8S.
- 17. Kasprzak KS, Diwan AB, Kaczmarek MZ, et al. Effects of ascorbic acid on carcinogenicity and acute toxicity of nickel subsulfide, and on tumor transplants growth in gulonolactone oxidase knock-out mice and wild-type C57BL mice. Toxicol Appl Pharmacol 2011;257(1):32-7.
- 18. Maniyar SA, Jargar JG, Das SN, et al. Alteration of chemical behavior of L ascorbic acid in combination with nickel sulfate at different pH solutions in vitro. Asian Pacific J Trop Biomed 2012;2(3):220-2.
- 19. Das KK, Buchner V. Effect of nickel exposure on peripheral tissue: role of oxidative stress in toxicity and possible protection by ascorbic acid. Rev Environ Health 2007;22(2):133-49.

- 20. Das KK, Jargar JG, Saha S. α Tocopherol supplementation prevents lead acetate and hypoxia induced hepatic dysfunction. Indian J Pharmacol 2015;47(3):285-91.
- 21. Das KK, Das SN, Dhundasi SA. Nickel, its adverse health effects & oxidative stress. Indian J Med Res 2008;128(4):412-25.
- 22. Sunderman FW, Kincaid JF. Nickel poisoning. II. Studies on patients suffering from acute exposure to vapors of nickel carbonyl. J Am Med Assoc 1954;155(10):889-94.
- 23. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for nickel. U.S. Department of Health and Human Services, Public Health Service, ATSDR. Atlanta, Georgia, USA: U.S. Government Printing Office; 2003. p. 5-16.
- 24. Weischer CH, Kordel W, Hochrainer D. Effects of NiCl2 and NiO in Wistar rats after oral uptake and inhalation exposure, respectively. Zentral Bakteriol Mikrobiol Hyg (B) 1980;171:336-51.
- 25. Ambrose AM, Larson PS, Borzelleca JR, Hennigar Jr GR. Long term toxicologic assessment of nickel in rats and dogs. J Food Sci Technol 1976;**13**:181–7.
- 26. Bouton CM, Frelin LP, Forde CE, et al. Synaptotagmin I is a molecular target for lead. J Neurochem 2001;76(6):1724–35.
- 27. Taylor CT. Mitochondria and cellular oxygen sensing in the HIF pathway. Biochem J 2008;409:19-26.
- 28. Kiang JG, Tsen KT. Biology of hypoxia. Chin J Physiol 2006;49(5):223-33.
- 29. Semenza GL, Nejfelt MK, Chi SM, Antonarakis SE. Hypoxia-inducible nuclear factors bind to an enhancer element located 3'to the human erythropoietin gene. Proc Natl Acad Sci USA 1991;88:5680-4.
- 30. Leonard SS, Harris GK, Shi XL. Metal-induced oxidative stress and signal transduction. Free Radic Biol Med 2004;37:1921–42.
- 31. Semenza GL. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. J Appl Physiol 2000;88:1474–80.
- 32. Vengellur A, LaPres JJ. The role of hypoxia inducible factor 1α in cobalt chloride induced cell death in mouse embryonic fibroblasts. *Toxicol Sci* 2004;82(2):638-46.
- 33. Chun YS, Kim MS, Park JW. Oxygen-dependent and independent regulation of HIF-1alpha. J Korean Med Sci 2002;17:581-8.
- 34. Tan HH, Fiel MI, Sun Q, et al. Kupffer cell activation by ambient air particulate matter exposure may exacerbate non-alcoholic fatty liver disease. J Immunotoxicol 2009;6(4):266-75.
- 35. Lin Y-C, Lian I-B, Kor C-T, et al. Association between soil heavy metals and fatty liver disease in men in Taiwan: a cross sectional study. BMJ Open 2017;**7**(1):e014215.
- 36. Sidhu P, Gorg ML, Morgenstern P, et al. Role of zinc in regulating the levels of hepatic elements following nickel toxicity in rats. Biol Trace Elem Res 2004;**102**:161–72.
- 37. Volini F, de la Huerga J, Kent G. Trace metal studies in the liver disease using atomic absorption spectrometry. In: Sunderman FW, Sunderman Jr FW, editors. Laboratory diagnosis of liver diseases. St. Louis, MO, USA: Warren H. Green Inc.; 1968. p. 199.
- 38. Sunderman Jr FW. Nickel. In: Merian E, Anke M, Ihnat M, Stoeppler M, editors. Metals and their compounds in the environment. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA; 1991. p. 841-67.
- 39. Cave M, Appana S, Patel M, et al. Polychlorinated biphenyls, lead, and mercury are associated with liver disease in American adults: NHANES 2003-2004. Environ Health Perspect 2010;118(12):1735-42.
- 40. Berrahal AA, Lasram M, El Elj N, et al. Effect of age-dependent exposure to lead on hepatotoxicity and nephrotoxicity in male rats. Environ Toxicol 2011;**26**(1):68–78.
- 41. Britton RS. Metal-induced hepatotoxicity. Semin Liver Dis 1996;16(1):3–12.
- 42. Sunderman Jr FW, Dingle B, Hopfer SM, Swift T. Acute nickel toxicity in electroplating workers who accidently ingested a solution of nickel sulfate and nickel chloride. Am J Ind Med 2007;14:257-66.
- 43. Das KK, Gupta AD, Dhundasi SA, et al. Effect of L-ascorbic acid on nickel-induced alterations in serum lipid profiles and liver histopathology of rats. J Basic Clin Physiol Pharmacol 2006;17:29-44.
- 44. U.S. Department of Health and Human Services (DHHS). Seventh annual report on carcinogens: summary 1994. Research Triangle Park, NC, USA: DHHS, National Institute of Environmental Health Sciences; 1994. p. 262-9.
- 45. Cross CE, van der Vliet A, O'Neill CA, Louie S, Halliwell B. Oxidants, antioxidants and respiratory tract lining fluids. Environ Health Perspect 1994;102:185-91.
- 46. Rodriguez RE, Misra M, North SL, Kasprzak KS. Nickelinduced lipid peroxidation in the liver of different strains of mice and its relation to nickel effects on antioxidant systems. Toxicol Lett 1991;57:269-81.
- 47. Das KK, Das SN, Dasgupta S. The influence of ascorbic acid on nickel induced hepatic lipid peroxidation in rats. J Basic Clin Physiol Pharmacol 2001;12:187-94.
- 48. Kantola T, Kivisto KT, Neuvonen PJ. Grapefruit juice greatly increases serum concentration of lovastatin and lovastatin acid. Clin Pharmacol Ther 1998;63:397-402.
- 49. Gupta AD, Das SN, Dhundasi SA, Das KK. Effect of garlic (Allium sativum) on heavy metal (nickel II and ChromiumVI) induced alteration of serum lipid profile in male albino rats. Int J Environ Res Public Health 2008;5(3):147–51.
- 50. Tikare S, Yendegiri SM, Dhundasi SA, et al. Protective effect of α-tocopherol against nickel sulfate induced hematotoxicity, hepatotoxicity and nephrotoxicity in male albino rats. *Indian J Physiol Pharmacol* 2013;**57**(03):280–92.
- 51. Das KK, Das SN, Dhundasi SA. Nickel: molecular diversity, application, essentiality and toxicity in human health. In: Blanc G, Moreau D, editors. Biometals, molecular structures, binding properties and applications. New York, USA: Nova Science Publishers Inc.; 2010. p. 33-58.
- 52. Cartana J, Arola L. Nickel-induced hyperglycaemia: the role of insulin and glucagon. Toxicology 1992;71(1-2):181-92.
- 53. Mathur AK, Gupta BN. Dermal toxicity of nickel and chromium in Guinea pigs. Vet Hum Toxicol 1994;36(2):131-2.
- 54. El-Saieed ME, Mekawy MM. Nickel toxicity in Oreochromis niloticus fish. J Egypt Soc Toxicol 2001;24:47–54.

- 55. Ptashynski MD, Klaverkamp JF. Accumulation and distribution of dietary nickel in lake white fish (Coregonus clupeaformis). Aquat. Toxicol 2002;58(3-4):249-64.
- 56. Sobecka E. Changes in the iron level in the organs and tissues of wels cat fish, silurus Glanis L. Caused by nickel. Acta Ichthyol Piscat 2001;31(2):127-43.
- 57. Pereira GJG, Molina SMG, Lea PJ, et al. Activity of antioxidant enzymes in response to cadmium in C. juncea. Plant Soil 2002;239:123–32.
- 58. Damek-Poprawa M, Sawicka-Kapusta K. Damage to the liver, kidney, and testis with reference to burden of heavy metals in yellow-necked mice from areas around steelworks and zinc smelters in Poland. Toxicology 2003;186(1-2):1-10.
- 59. Isojärvi JI, Pakarinen AJ, Rautio A, et al. Liver enzyme induction and serum lipid levels after replacement of carbamazepine with oxcarbazepine. Epilepsia 1994;35(6):1217-20.
- 60. Marklund SL. Superoxide dismutase in human tissue cells and extracellular fluids, clinical implication. In: Liss AR, editor. Free radicals aging and degenerative disease. New York: Raven Press; 1986. p. 509.
- 61. Khalaf AA, Moselhy WA, Abdel-Hamed MI. The protective effect of green tea extract on lead induced oxidative and DNA damage on rat brain. Neurotoxicology 2012;33:280-9.
- 62. Cadenas E. Oxidation stress. New York, NY, USA: Academic Press; 1985. p. 313-30.
- 63. Baeuerle PA, Baltimore D. NF-kappa B: Ten years after. Cell 1996;87:13-20.
- 64. Souza V, Bucio L, Gutiérrez-Rui MC. Cadmium uptake by a human hepatic cells line (WRL-68). Toxicology 1997;120:215-20.
- 65. Fujishiro H, Okugaki S, Kubota K, Fujiyama T, Miyataka H, et al. The role of ZIP8 down-regulation in cadmium-resistant metallothionein-null cells. J Appl Toxicol 2009;29:367-73.
- 66. Horiguchi H, Harada A, Oguma E, et al. Cadmium-induced acute hepatic injury is exacerbated in human interleukin-8 transgenic mice. Toxicol Appl Pharmacol 2000;163:231-9.
- 67. Marth E, Burt S, Jelovcan S. Influence of cadmium on the immune system description of stimulating reactions. Cent Eur J Public Health 2000;8:40-4.
- 68. Ahmed M, Akhter MJ, Alhadlaq HA, et al. Comparative cytotoxic response of nickel ferrite nanoparticles in human liver HepG2 and breast MFC-7 cancer cells. Chemosphere 2015;135:278-88.
- 69. Jungermann K, Kietzmann T. Oxygen: modulator of metabolic zonation and disease of the liver. Hepatology (Baltimore, Md.) 2000;31:255-60.
- 70. Nieminen AL, Gores GJ, Wray BE, et al. Calcium dependence of bleb formation and cell death in hepatocytes. Cell Calcium 1988;9:237-46.
- 71. Sewerynek E, Reiter RJ, Melchiorri D, et al. Oxidative damage in the liver induced by ischemia-reperfusion: protection by melatonin. Hepatogastroenterology 1996;43:898-905.
- 72. Tanaka H, Yamamoto M, Hashimoto N, et al. Hypoxia-independent overexpression of hypoxia-inducible factor 1alpha as an early change in mouse hepatocarcinogenesis. Cancer Res 2006;66:11263-70.
- 73. Ju C, Colgan SP, Eltzschig HK. Hypoxia-inducible factors as molecular targets for liver diseases. J Mol Med 2016;94(6):613–27.
- 74. Alchera E, Tacchini L, Imarisio C, et al. Adenosine-dependent activation of hypoxia-inducible factor-1 induces late preconditioning in liver cells. Hepatology 2008;48:230-9.
- 75. Guo JY, Yang T, Sun XG, et al. Ischemic postconditioning attenuates liver warm ischemia-reperfusion injury through Akt-eNOS-NO-HIF pathway. J Biomed Sci 2011;18:79.
- 76. Nishiyama Y, Goda N, Kanai M, et al. HIF- 1alpha induction suppresses excessive lipid accumulation in alcoholic fatty liver in mice. J Hepatol 2012;56:441-7.
- 77. Byrne CD. Hypoxia and non-alcoholic fatty liver disease. Clin Sci 2010;118(6):397-400.
- 78. Nieminen AL, Saylor AK, Herman B, et al. ATP depletion rather than mitochondrial depolarization mediates hepatocyte killing after metabolic inhibition. Am J Physiol 1994;267:C67-74.
- 79. Gores GJ, Nieminen AL, Wray BE, et al. Intracellular pH during "chemical hypoxia" in cultured rat hepatocytes. Protection by intracellular acidosis against the onset of cell death. J Clin Investig 1989;83:386-96.
- 80. WHO. National policy on traditional medicine and regulation of herbal medicines. 2005.
- 81. Goyer RA, Clarkson TW. Toxic effects of metals. In: Klaassen C, editor. Casarett and Doull's toxicology: the basic science of poisons. 6th ed. New York, NY, USA: McGraw-Hill Health Professions Division; 2001. p. 822-6.
- 82. Prasanthi R, Devi CB, Basha DC, et al. Calcium and zinc supplementation protects lead (Pb)-induced perturbations in antioxidant enzymes and lipid peroxidation in developing mouse brain. Int J Dev Neurosci 2010;28:161-7.
- 83. Ryu DY, Lee SJ, Park DW, et al. Dietary iron regulates intestinal cadmium absorption through iron transporters in rats. Toxicol Lett 2004;152:19–25.
- 84. Djukić-Ćosić D, Ninković M, Maličević Z, et al. Effect of magnesium pretreatment on reduced glutathione levels in tissues of mice exposed to acute and subacute cadmium intoxication: a time course study. Magnes Res 2007;20:177-86.
- 85. Basha DC, Rani MU, Devi CB, et al. Perinatal lead exposure alters postnatal cholinergic and aminergic system in rat brain: reversal effect of calcium co-administration. Int J Dev Neurosci 2012;30:343-50.
- 86. Das KK, Dhundasi SA, Das SN. Hexavalent chromium and its effect on health: possible protective role of garlic (Allium sativum Linn). J Basic Clin Physiol Pharmacol 2011;**22**(1–2):3–10.
- 87. Vimal V, Devaki T. Hepatoprotective effect of allicin on tissue defense system in galactosamine/endotoxin challenged rats. J Ethnopharmacol 2004;90(1):151-4.
- 88. Garlic: Nature's amazing nutritional and medicinal wonder food. P.O.Box 160, Pleasant Grove, UT 84062: Woodland Publishing Inc.; 1995. p. 5–25.
- 89. Weil A. Natural health, natural medicine. Boston: Houghton-Mifflin Company; 1990. p. p237.
- 90. Simon JA, Hudes ES. Relationship of ascorbic acid to blood lead levels. JAMA 1999;281:2289–93.
- 91. Goyer RA, Cherian MG. Ascorbic acid and EDTA treatment of lead toxicity in rats. Life Sci 1979;24:433-8.

- 92. Nemmiche S, Chabane-Sari D, Guiraud P. Role of α-tocopherol in cadmium-induced oxidative stress in Wistar rat's blood, liver and brain. Chem Biol Interact 2007;170:221-30.
- 93. Reddy SY, Pullakhandam R, Kumar BD. Thiamine reduces tissue lead levels in rats: mechanism of interaction. Biometals 2010;23:247-53.
- 94. Shi J, Maguer ML. Lycopene in tomatoes: chemical and physical properties affected by food processing. Crit Rev Food Sci Nutr 2000;40:1–42.
- 95. Pires VC, Gollücke A, Ribeiro DA, et al. Grape juice concentrate protects reproductive parameters of male rats against cadmium-induced damage: a chronic assay. Br J Nutr 2013;110:2020-9.
- 96. Mantur VS, Sommanavar MS, Yendegiri SM, et al. Ameliorating effect of black tea extracts on cadmium chloride -induced alteration of serum lipid profile and liver histopathology in rats. Indian J Physiol Pharmacol 2014;58(2):128–32.
- 97. Haleagrahara N, Jackie T, Chakravarthi S, et al. Protective effects of Etlingera elatior extract on lead acetate-induced changes in oxidative biomarkers in bone marrow of rats. Food Chem Toxicol 2010;48:2688-94.
- 98. Dewanjee S, Sahu R, Karmakar S, et al. Toxic effects of lead exposure in Wistar rats: involvement of oxidative stress and the beneficial role of edible jute (Corchorus olitorius) leaves. Food Chem Toxicol 2013;55:78-91.
- 99. Halttunen T, Collado M, El-Nezami H, et al. Combining strains of lactic acid bacteria may reduce their toxin and heavy metal removal efficiency from aqueous solution. Lett Appl Microbiol 2008;46:160-5.
- 100. Tian F, Zhai Q, Zhao J, et al. Lactobacillus plantarum CCFM8661 alleviates lead toxicity in mice. Biol Trace Elem Res 2012;150:264-71.
- 101. Goldhaber SB. Trace element risk assessment: essentiality vs. toxicity. Regul Toxicol Pharmacol 2003;38:232–42.
- 102. Sneddon AA, Wu HC, Farquharson A, et al. Regulation of selenoprotein GPx4 expression and activity in human endothelial cells by fatty acids, cytokines and antioxidants. Atherosclerosis 2003;171(1):57-65.
- 103. Sagun KC, Carcamo JM, Golde DW. Vitamin C enters mitochondria via facilitative glucose transporter 1(glut-1) and confers mitochondrial protection against oxidative injury. FASEB J 2005;19(2):1657-67.
- 104. Korashy HM, El-Kadi AO. The role of redox-sensitive transcription factors NF-kappaB and AP-1 in the modulation of the Cyp1a1 gene by mercury, lead, and copper. Free Radic Biol Med 2008;44(5):795–806.
- 105. Kelly MJ, Richardson W. Possible mechanisms for the protective action of alpha-tocopherol in vascular hypoxia. J Auton Pharmacol 1996; 16(2):87–95.
- 106. Wang GL, Jiang BH, Rue EA, et al. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci USA 1995;92:5510-4.
- 107. Novo E, Cannito S, Zamara E, et al. Proangiogenic cytokines as hypoxia-dependent factors stimulating migration of human hepatic stellate cells. Am J Pathol 2007;170:1942-53.
- 108. Das KK, Nemegouda SR, Patil SG, et al. Possible hypoxia signaling induced alteration of glucose homeostasis in rats exposed to chronic intermittent hypoxia - role of antioxidant (vitamin C) and Ca2+ channel blocker (cilnidipine). Curr Signal Transduct Ther 2016;11(1):49-55.
- 109. Semenza GL. HIF-1: upstream and downstream of cancer metabolism. Curr Opin Genet Dev 2010;20:51-6.
- 110. Bell EL, Klimova TA, Eisenbart J, et al. The Qo site of the mitochondrial complex III is required for the transduction of hypoxic signaling via reactive oxygen species production. J Cell Biol 2007;177:1029–36.

Dietary Interventions in Liver Disease

Foods, Nutrients, and Dietary Supplements

Edited by Ronald Ross Watson and Victor R. Preedy

Dietary Interventions in Liver Disease: Foods, Nutrients, and Dietary Supplements provides valuable insights into the agents that affect metabolism and other health-related conditions in the liver. It provides nutritional treatment options for those suffering from liver disease. Information is presented on a variety of foods including herbs, fruits, soy, and olive oil showing that changes in intake can change antioxidants and disease-preventing nonnutrients, affecting liver health and/or disease promotion. This book serves as a valuable resource for biomedical researchers who focus on identifying the causes of liver diseases as well as food scientists targeting health-related product development.

Key Features:

- Provides information on agents that affect metabolism and other health-related conditions in the liver.
- Explores the impact of composition, including differences based on country of origin and processing techniques, to highlight compositional differences and their effect on the liver.
- Addresses the most positive results from dietary interventions using bioactive foods to impact liver disease, including reduction of inflammation and improved function.





