ejpmr, 2021,8(8), 228-237.

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

BIOINFORMATIC ANALYSIS OF SELECTED PHYTOCHEMICALS, NATURAL COMPOUNDS AND PROTEINS FOR CIRRHOSIS

Manish Kumar[1], Sachin Verma[1], Mohit Mishra[1], Khushboo Rana[1], Mishka[1], Varsha Prajapati[1], Noopur Khare[2,3], Abhimanyu Kumar Jha[1,2] and Neha Prakash Rai[1]*

[1]Department of Biotechnology, Faculty of Life Sciences, Institute of Applied Medicines and Research, Ghaziabad, Uttar Pradesh, India.

[2]Institute of Technology and Management, Meerut, Uttar Pradesh, Affiliated to Dr. A.P.J. Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India.

[3]Shri Ramswaroop Memorial University, Barabanki, Uttar Pradesh, India.

***Corresponding Author: Neha Prakash Rai**

Department of Biotechnology, Faculty of Life Sciences, Institute of Applied Medicines and Research, Ghaziabad, Uttar Pradesh, India.

Article Received on 03/06/2021 **Article Revised on 24/06/2021** **Article Accepted on 14/07/2021**

ABSTRACT

Cirrhosis is also called liver cirrhosis or hepatic cirrhosis and end-stage liver disease. Cirrhosis results in approximately 200,000 deaths per year in India, primary biliary cholangitis, and primary sclerosing cholangitis which can disrupt bile duct function, genetic disorders. Symptoms can include fluid build-up in the abdomen, jaundice, bruising easily, itchiness, swelling in the lower legs, and the development of spider-like blood vessels in the skin. Cirrhosis is also known to occur at the late stage of liver damage. The early stages of the liver disease led to the inflammation in the liver. It considers 4 stages in the early stages of liver disease. Several phytochemicals and natural compounds are used for the treatment of cirrhosis such as Alpha Hederin, Berberine, Curcumin, Epigallocatechin-3-Gallate, Ferulic Acid, Genistein, Ginkgolide, Luteolin, Oleanic Acid, Quercetin, Resveratrol, Thiophenes and Sulfonamides, Benzimidazole and Lidamycin. α-Hederin was present in attenuate hepatotoxicity in mice which can be induced due to several liver toxicants. Luteolin is a type of flavone that was chemically known as 2-(3,4-dihydroxy phenyl)-5,7-dihydroxychromen-4-one and may predominantly present in several types of plants, flowers, and fruits. The auxin binding protein is a family of proteins that can bind with auxin.

KEYWORDS: Cirrhosis, Alpha Hederin, Luteolin, RARB and Auxin binding protein.

INTRODUCTION

Cirrhosis is also known as liver cirrhosis, hepatic cirrhosis, and end-stage liver disease, in which liver disease causes liver function to deteriorate.[1] They were replaced by the normal functioning of tissue over time and leading to the impaired liver function of cirrhosis. It may develop slowly over months or years.[2,3] Decompensating may be defined as the development of ascites, complication portal is hypertensive, gastrointestinal (GI) bleeding, and jaundice.[4] Cirrhosis is considered through compensated and decompensated stages, with several features of prognoses and predictors of death.[5] Cirrhosis consists of approximately 200,000 deaths in a year in India. Liver transplantation is improving the longevity[6], but every people was not taken this transplantation treatment because it does not have the majority of the patients.[7] Cirrhosis affected about 2.8 million people in a year and resulted in 1.3 million deaths in 2015.[8, 9] In tUnited States, Men die more of cirrhosis as compared to women.[3] The first known condition was occurring due to Hippocrates' description in the 5th century BCE.[10] The term cirrhosis first time was introduced in 1819, from a Greek word of yellowish color in liver disease.[11] Cirrhosis is caused due to alcoholic liver disease, non-alcoholic steatohepatitis (NASH) – (the progressive form of non-alcoholic fatty liver disease), chronic hepatitis B, and chronic hepatitis C.[12, 14] Heavy drinking over several years can cause alcoholic liver disease.[15] NASH having several causes, including obesity, high blood pressure, abnormal levels of cholesterol, type 2 diabetes, and metabolic syndrome.[13] Less common types of causes in cirrhosis include autoimmune hepatitis system, their primary biliary cholangitis activity, and primary sclerosing cholangitis which can disrupt bile duct function, genetic disorders such as Wilson's disease and hereditary hemochromatosis, and chronic heart failure with liver congestion.[12]

Early symptoms may include loss of appetite, unexplained weight loss, tiredness, weakness, nausea and vomiting, and discomfort in the right upper quadrant of the abdomen.[16] As the disease, symptoms can include fluid build-up in the abdomen, jaundice, bruising

easily, itchiness, swelling in the lower legs, and the development of spider-like blood vessels in the skin.[17]

CAUSES

Cirrhosis can cause many cases worldwide.[18] Globally, 57% of cases of cirrhosis of hepatitis B (30%) or hepatitis C (27%) worldwide.[19] Alcohol is the most important reason to cause cirrhosis and consider 20-40% of cases worldwide.[19, 20]

Alcoholic liver disease (ALD). Alcoholic cirrhosis develops in about 10–20% of individuals.[21] Alcohol seems to damage and injure the liver due to blocking of their normal activity of carbohydrates, protein, and fats. The acetaldehyde damage formation from alcohol was reactive but may lead to the accumulation of other reactive products in their liver.[20, 22]

Non-alcoholic fatty liver disease (NAFLD). In NAFLD, it is a fat builds up type in the liver which can cause by scar tissue. It is similar to alcoholic liver disease, but there is no history of notable alcohol use. Blood tests and medical imaging are used to diagnose NAFLD and NASH and sometimes a liver biopsy is required.[23]

Chronic hepatitis C. It causes several inflammations which damage led to cirrhosis. About 20–30% of patients were affected by chronic hepatitis C which was developing cirrhosis disease.[24-26]

Symptoms

Cirrhosis can take a long time for developing the symptoms which may be slow to emerge. Early symptoms can involve; loss of appetite, unexplained weight loss, nausea and sickness, tiredness, weakness, and discomfort in the upper right abdomen.[12] The other signs and symptoms can develop like as cognitive impairments, confusion, memory loss, sleep disorders, and personality changes. Further decline may result in a build-up of fluid in the lower legs and feet; severe bloating of the abdomen from a fluid build-up known as ascites; jaundice; severe itchy skin, and darkly colored urine.[12] Some of these symptoms involve secondary subsequent portal hypertension which may enhance blood pressure in the blood supply to the liver.[22]

Liver dysfunction

The following features involve in liver functioning.

- Spider angiomata or spider nevi was consisting many smaller vessels for enhancing the estradiol in the central arteriole.[27]
- Palmar erythema is a reddening of palms at which was seen about 23% of cirrhosis cases[28] for enhancing estrogen.[29]
- Gynecomastia was enhancing the breast size in men by increasing the within 2/3 of cases.[30-32]
- Hypogonadism was affecting the male sex hormones including infertility, loss of sexual drive, and testicular atrophy. Hypogonadism may consider cirrhosis by iron overload and alcoholism.[33]
- Jaundice is a yellow discoloration of the skin and mucous membranes , increased levels of bilirubin.[20]

Portal hypertension

Liver cirrhosis can increase the resistance of blood flow which may lead to higher pressure in the portal venous system. An enlarged type of spleen was present in 35% to 50% of cases in worldwide.[22]

Stages of Cirrhosis

- Cirrhosis is also called the late stage of liver damage. It was caused due to inflammation of liver disease which can lead to scarring (fibrosis) but not treatment.
- In the stages of cirrhosis, many complications can develop .It is end-stage liver disease (ESLD), and liver transplantation treatment occur.
- **Stage 1**

It may involve in several type of scarring in liver with few symptoms.

It can develop portal hypertension.

- **Stage 3**

It can involve with development of swelling abdomen with high liver scarring. It can decompensate through serious complications with possible type of liver failure.

- **Stage 4**

It can be life threatening process and people can develop end-stage liver disease (ESLD) without a transplant.

Role of Phytochemicals Against Cirrhosis

- **Alpha Hederin**

α-Hederin is a type of oleanane-type saponin that may present in *Nigella sativa* and *Hedera helix* types of plants and occur benefits in the respiratory diseases. α-Hederin was present in attenuate hepatotoxicity in mice which can be induced due to APAP with CYPB5, CYP1A, CYP450, CYP2A, and CYP3A enzymes. α-Hederin has reduced the activities of oxidation of testosterone, pentoxyresorufin-*O*-dealkylation, coumarin-7-hydroxylation, ethoxyresorufin-*O*-dealkylation, chlorzoxazone-6-hydroxylation and α-hydroxyltestosterone, androstenedione, and dehydroxytestosterone.[34]

- **Berberine**

It is a type of alkaloid chemically known as 3-benzodioxolo (5,6-a) quinolizinium sulfate 5, 6-dihydro-9,10-dimethoxybenzo(g)-1, and *Berberis aristata* like plant and study depend upon pharmacological properties, including hepatoprotective. (Janbaz and Gilani., 2009) were shown their result against hepatoprotective effects in APAP-induced hepatotoxicity.[35] They also enhanced the strychnine-induced toxicity and pentobarbital-induced sleeping time which inhibitory the effect of CYPs metabolizing enzymes.[35] Recently, (Vivoli et al., 2016) will be shown experimental models such as APAP-induced liver toxicity activity, methionine, and their choline-deficient diet-induced steatohepatitis.[36]

The activation of inflammasomes was APAP-induced hepatotoxicity which seems to inhibit the activity of inflammation and helps to cure hepatocyte injury, immune cell activation system, and amplification of inflammation and cell death. Since inhibiting the activation of P2X7 and their purinergic receptors which can mediate the activity of inflammasome activation due to berberine appears a novel approach.[36]

- **Curcumin**

It is a type of yellow polyphenol pigment which is chemically known as (1E, 6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione. It is a bioactive phytochemical in the rhizomes of *Curcuma longa* and is called turmeric which is used for dietary and cosmetic purposes. The protection of curcumin affects liver injury which involves inflammation, and cell death. The cytoprotective effect of curcumin against APAP was obtained through rat hepatocytes due to attenuating lipid peroxidation, but there is no side effect. Thus, higher doses of the drug may cure the effects against curcumin.[37] It shows protective effects against a therapeutic dose of NAC.[38, 39]

- **Epigallocatechin-3-Gallate**

It is also called epigallocatechin gallate. It is a type of ester with gallic acid and epigallocatechin of catechin. Catechin was found in tea which is a type of polyphenol under research for the potential of human health and disease effect. It was used as a source of dietary supplements. It can decrease the APAP-glucuronate and -glutathione contents through plasma and liver.[44]

- **Ferulic Acid**

Ferulic acid is a type of hydroxycinnamic acid which is an organic compound and its structure resemble to curcumin and abundantly phenolic phytochemicals may found in plant cell walls and seeds of many vegetables, fruits, and cereals like as brown rice, whole wheat, and oats. It was a precursor of aromatic compounds which was derived from the ferula genus. According to Wand and Penf (1994) was obtained the activity of hepatoprotective of sodium ferulate which was an active ingredient of *Angelica sinensis* Diels.[45]

Genistein

- It is a type of natural compound that belongs to the isoflavones class. It inhibits angiogenesis and phytoestrogen. It was used to promoted APAP glucuronidation due to activation of UGTs activity and glutathione peroxidase and inhibiting CYP2E1.[47,48] Genistein was used as a derivative of APAP formation with excretion into bile which may arise through inhibition of sinusoidal efflux transport.[49, 50]

- **Ginkgolide**

Ginkgolide A is a type of terpenic lactone natural occurring compound which is commonly known as 9H-1,7a-(Epoxymethano)-1H,6aH-cyclopenta(c) furo(2,3-b), and found in *Ginkgo biloba* which is used as a dietary supplement for the therapeutic benefits. It has a 20-carbon skeleton with diterpenoids and may synthesize from geranylgeranyl pyrophosphate. Ginkgolide A showed their effect against APAP toxicity within hepatocytes which was isolated from adult male Long-Evans rats. On the other hand, there are several types of derivatives like ginkgolide J, quercetin, isorhamnetin, ginkgolide B, ginkgolide C, kaempferol, and isorhamnetin-3-*O*-rutinoside which may fail to affect LDH leakage by APAP.[51, 52]

Role of Natural Compound In Cirrhosis

- **Luteolin**

Luteolin is a type of flavone that is chemically known as 2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one and may predominantly present in several types of plants, flowers, and fruits. It is beneficial for health including liver diseases. Luteolin is considered for inhibiting the sulfation in liver cytosolic.[53,54] Luteolin is used for the process of restored liver enzymes, inhibited lipid peroxidation activity.

- **Oleanolic Acid**

Oleanolic acid (OA) is a type of pentacyclic triterpene which was chemically known as 3-β-3-Hydroxyolean-12-en-28-oic acidic and present in medicinal plants which are used in traditional Chinese medicine. On the other hand, OA is found to ameliorate hepatotoxicity induced through chemical toxicants, including APAP.[58] The authors found that OA reduced the mouse liver YP1A and CYP2A enzymes. It was enhanced the GSH content in the liver along with the GSH peroxidase effect and GSH reeducates.[59] The hepatoprotective activities of OA were reconfirmed for prevented APAP-induced GSH levels in the liver along with mortality reduced.[60] OA has increased its expression in metallothionein and glutamate-cysteine ligases (Gclc and Gclm) in the liver.[61] Reisman et al. (2009) was confirmed the protection of the OA liver through Nrf2-dependent and Nrf2-independent mechanisms which can contributes to hepatoprotection.[62, 63]

- **Quercetin**

It is a type of plant flavanol that is found in many vegetables, seeds, fruits, and grains; also, in red onions and kale food. It is obtained from the flavonoid group of polyphenols. It is also a bitter flavor that is used as an ingredient in dietary supplements, beverages, and foods. Gilani et al. (1997) first described the activity of hepatoprotective in quercetin[64] and reduced the toxicity of APAP-induced liver by repletion of GSH.[65,66] Quercetin-3, 7-dimethyl-ether was also a derivative that was obtained by leaves of *Cistus laurifolius* L. It is protected APAP-induced liver toxicity through antioxidant action.[68] Quercetin was present in ameliorating APAP-induced liver injury due to restoring their liver enzymes and antioxidants, which inhibiting the lipid peroxidation concomitant to histological salvage.[69] Thus, quercetin and chrysin were enhancing

the systemic exposure of APAP due to inhibiting intestinal *P*-glycoprotein and metabolism of APAP.[70] The optimized quercetin formulation showed their result to enhance the solubility and dissolution in displayed potent protection due to biochemical improvement against APAP-induced hepatotoxicity.[71] It was used to enhance the expression of p62 siRNA and their activated JNK in hepatocytes.[72]

- **Resveratrol**

Resveratrol is a type of polyphenol compound of the stilbene group which is chemically known as 3, 4, 5-trihydroxystilbene, and present in berries, nuts, grapes, and beverages. On other hand, resveratrol occurs treatment with protective against APAP-induced liver injury in CD-1 mice which observation the Th1-dominant response in Th1/Th2 cytokine balance.[76] It was present to inhibit the downstream nuclear DNA fragmentation which was out through apoptosis-inducing factor and endonuclease G from the activity of mitochondria independent of Bax pore formation.[75]

Thiophenes

It is a type of heterocyclic compound and consists C4H4S formula and planar five-membered ring. It is a common aromatic by extensive substitution reactions. It is a colorless liquid within a benzene-like odor and resembles some reaction like benzene. Thiophene analogous compounds can include Pyrrole (C4H4NH), Selenophene (C4H4Se), and Furan (C4H4O) which may vary by heteroatom in the ring.

It is widely used for building blocks in many pharmaceuticals and agrochemicals.[80] The biologically active compound of the benzene ring can be replaced through thiophene without loss of activity.[81] For Example NSAID Iornoxicam and thiophene analog of fentanyl, piroxican, and sufentanil.

Thiophene was discovered by Victor Meyer in 1883 as a contaminant in benzene.[82] It was isolated by isatin forms a blue dye which mixed with sulfuric acid and crude benzene. This reaction from the blue indophenin was long believed for a reaction with benzene.

- **Sulfonamides**

The thiazide diuretics and sulfonylureas both are new synthetic drug groups based on antibacterial sulfonamides.[83, 84]

Prontosil as Bayer named the new drug was first discovered the medicine which was effectively treating a range of bacterial infections inside the body. It acts as competitive inhibitors of the enzyme dihydropteroate synthase (DHPS), an enzyme involved in folate synthesis. They also inhibit the growth and multiplication of bacteria but do not kill them. In humans, bacteria acquire folate (vitamin B9) by diet.[85] It is used as an antibiotic for the treatment of inflammatory bowel disease and Cirrhosis.[86]

Benzimidazole

Benzimidazole is a type of heterocyclic aromatic organic compound and consists of the fusion of benzene and imidazole for bicyclic compound and it was colorless solid. It was produced by condensation of O-Phenylene diamine within formic acid. Benz imidazole is used for a variety of therapeutic uses including cirrhosis, antifungal, antitumor, antiviral, antiphrastic, antihistamine as well as neurology endocrinology, orthamology, and cardiovascular disease.

Historically, the first benzimidazole was prepared by Hoebrecker in 1872 who consider 2, 5 (or 2, 6)-dimethylbenzimidazole through the reduction of 2-nitro-4-methylac entanilide.[87] The first treatment of benzimidazole was started many years ago in 1990 was started onwards, which synthesis number of benzimidazole were reported and there resulted in increased stability bioavailability and significant biological activity.

Lidamycin

Lidamycin is a type of antitumor antibiotic that consists complex of an enediyne chromophore and an apoprotein.[88-91] It was shown antibiotic activity against the gram-positive bacteria.[92] It was cytotoxic molecules known for induction of a higher ratio of DNA double-strand breaks than single-strand breaks.

It is a member of the enediyne anticancer antibiotic family which emphasis the discovery of their structure-activity and biological properties relationship.

Role of Selected Protein In Cirrhosis

- **Retinoic Acid Receptor Beta (Rarb)**

RARB binds heterodimers to their targets which respond to the elements in their response ligands, all-trans or 9-cis retinoic acid, and regulate their gene expression in several biological processes. The RXR/RAR heterodimers may bind with retinoic acid response elements (RARB) and are composed of tandem 5'-AGGTCA-3' sites which are called DR1-DR5.

In the absence and presence of hormone ligand, it may act as an activator of gene expression by weak binding to corepressors. RAR and RXR subtypes of RARB were knocked out by homologous recombination which determines their functions at the time of embryonic development in the adult.

RARB is also known as NR1B2 (nuclear receptor subfamily 1, group B, Member 2) which is a type of nuclear receptor encoded by the RARB gene in humans.[93, 94] The RARB encodes a gene found in a member of the thyroid hormone receptor subfamily of nuclear transcriptional regulators.

The RARB is an active form of Vitamin A that can mediate their cellular signaling through cell growth and differentiation and embryonic morphogenesis. They have

limits to the growth of several cell types through regulating gene expression.

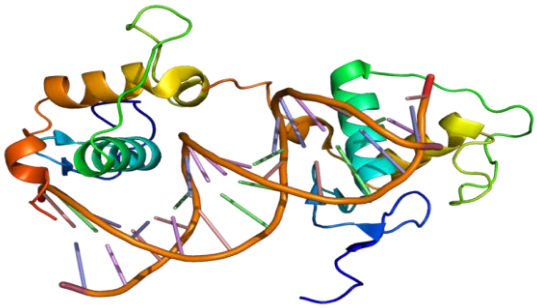

Figure 1: Crystal Structure of RARB Protein

- **Auxin Binding Protein 1 (Abp1)**

The auxin binding protein is a family of proteins that can bind with auxin.[95] It was present in the lumen of the endoplasmic reticulum [ER]. The primary structure leads an N-terminal hydrophobic leader sequence of 30-40 amino acids which representing a signal of translocation in protein to the ER.[96, 97] They contained 165 residues and may also contain several potential N-glycosylation sites.

ABP1 is used for the activation of two antagonizing ROP GTPase Signaling pathways which can involve cytoskeletal reorganization and cell shape formation. It can regulate the clathrin-mediated endocytosis to subsequently affect the PIN protein distribution. They consist of 4 amino acids sequence i.e., Lys-Asp-Glu-Leu at the C-terminus. It is used for growth and developmental responses.

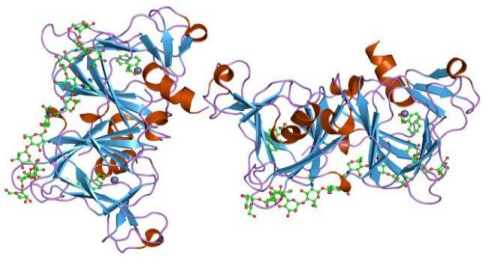

Figure 2: Crystal Structure of Auxin Binding Protein 1 (ABP1).

CONCLUSION

Natural Medicine is a very effective approach to treat cirrhosis or liver diseases. Naturopathy is developing rapidly for clinical practice and theoretical research. Natural agents have different types of therapeutic effects which depend on antioxidant, antiviral, anti-inflammatory, and antitoxic properties. On the other hand, natural medicines inhibiting the protein against cirrhosis which causes disease and also lack regulators with no side effects and cheaper prices which make them easy to get and use.

The advent of liver transplantation is successful with effective treatment for patients with end-stage liver diseases.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

ACKNOWLEDGEMENT

The authors acknowledge the help provided by the Department of Biotechnology, Faculty of Life Sciences, Institute of Applied Medicines and Research, Ghaziabad, Uttar Pradesh, India.

REFERENCES

1. "Cirrhosis". nhs.uk. 29 June 2020. Retrieved 8 February 2021.
2. Sherlock's diseases of the liver and biliary system. Dooley, James (James S.),, Lok, Anna S. F.,, Garcia-Tsao, Guadalupe,, Pinzani, Massimo (Thirteenth ed.). Hoboken, NJ. p. 82. ISBN 978-1-119-23756-3. OCLC 1019837000.
3. "Cirrhosis". National Institute of Diabetes and Digestive and Kidney Diseases. April 23, 2014. Archived from the original on 9 June 2015. Retrieved 19 May 2015.
4. Suk K.T. Hepatic venous pressure gradient: clinical use in chronic liver disease. Clin Mol Hepatol, 2014; 20: 6–14. [PMC free article] [PubMed] [Google Scholar].
5. D'Amico G., Garcia-Tsao G., Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol, 2006; 44: 217–231. [PubMed] [Google Scholar]
6. O'Brien J., Triantos C., Burroughs A.K. Management of varices in patients with cirrhosis. Nat Rev Gastroenterol Hepatol, 2013; 10: 402–412. [PubMed] [Google Scholar]
7. Tsochatzis E.A., Bosch J., Burroughs A.K. New therapeutic paradigm for patients with cirrhosis. Hepatology, 2012; 56: 1983–1992. [PubMed] [Google Scholar]
8. GBD 2015 Disease and Injury Incidence and Prevalence, Collaborators. (8 October 2016). "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study, 2015". Lancet, 388(10053): 1545–1602. doi:10.1016/S0140-6736(16)31678-6. PMC 5055577. PMID 27733282.
9. GBD 2015 Mortality and Causes of Death, Collaborators. (8 October 2016). "Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015". Lancet,

388(10053): 1459–1544. doi:10.1016/s0140-6736(16)31012-1. PMC 5388903. PMID 27733281.
10. Brower, Steven T. (2012). Elective general surgery : an evidence-based approach. New York: McGraw-Hill Medical. p. 36. ISBN 9781607951094. Archived from the original on, 2017-09-08.
11. Roguin A (2006). "Rene Theophile Hyacinthe Laënnec (1781–1826): The Man Behind the Stethoscope". Clinical Medicine & Research, 4(3): 230–5. doi:10.3121/cmr.4.3.230. PMC 1570491. PMID 17048358.
12. "Symptoms & Causes of Cirrhosis | NIDDK". National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved 8 February 2021.
13. "Definition & Facts of NAFLD & NASH | NIDDK". National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved 9 March 2021.
14. GBD 2013 Mortality and Causes of Death, Collaborators (17 December 2014). "Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013". Lancet, 385(9963): 117–71. doi:10.1016/S0140-6736(14)61682-2. PMC 4340604. PMID 25530442.
15. "Alcoholic liver disease: MedlinePlus Medical Encyclopedia". medlineplus.gov.
16. "Symptoms & Causes of Cirrhosis | NIDDK". National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved 8 February 2021.
17. "Definition & Facts for Cirrhosis | NIDDK". National Institute of Diabetes and Digestive and Kidney Diseases.
18. Ferri, Fred F. (2019). Ferri's clinical advisor 2019: 5 books in 1. Philadelphia, PA, 337–339. ISBN 9780323530422.
19. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP (October 2006). "The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide". J. Hepatol, 45(4): 529–38. doi:10.1016/j.jhep.2006.05.013. PMID 16879891.
20. Longo, Dan L.; et al., eds. (2012). Harrison's principles of internal medicine (18th ed.). New York: McGraw-Hill. pp. Chapter 308. Cirrhosis and Its Complications. ISBN 9780071748896.
21. Alcohol-Induced Liver Disease; "Alcohol Related Liver Disease and Alcohol Damage – ALF". Archived from the original on 2012-01-12. Retrieved 2012-01-25.
22. Friedman LS (2014). Current medical diagnosis and treatment 2014. [S.l.]: Mcgraw-Hill. pp. Chapter 16. Liver, Biliary Tract, & Pancreas Disorders. ISBN 978-0071806336.
23. "Diagnosis of NAFLD & NASH | NIDDK". National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved 9 March 2021.
24. Longo, Dan L.; et al., eds. (2011). Harrison's principles of internal medicine (18th ed.). New York: McGraw-Hill. p. Liver Transplantation. ISBN 9780071748896.
25. Edwards, CQ; Kushner, JP (Jun 3, 1993). "Screening for hemochromatosis". The New England Journal of Medicine, 328(22): 1616–20. doi:10.1056/NEJM199306033282208. PMID 8110209.
26. Tanner, MS (May 1998). "Role of copper in Indian childhood cirrhosis". The American Journal of Clinical Nutrition, 67(5 Suppl): 1074S–1081S. doi:10.1093/ajcn/67.5.1074S. PMID 9587155.
27. Li CP, Lee FY, Hwang SJ, et al. (1999). "Spider angiomas in patients with liver cirrhosis: role of alcoholism and impaired liver function". Scand. J. Gastroenterol, 34(5): 520–3. doi:10.1080/00365529750026272. PMID 10423070.
28. "Palmar erythema | DermNet NZ". dermnetnz.org.
29. William, James (2005). Andrews' Diseases of the Skin: Clinical Dermatology. Saunders. ISBN 978-0-7216-2921-6.
30. Slater, Joseph S. Esherick, Daniel S. Clark, Evan D. (2012-12-18). Current practice guidelines in primary care 2013. New York: McGraw-Hill Medical. pp. Chapter 3: Disease Management. ISBN 978-0071797504.
31. Van Thiel, DH; Gavaler, JS; Schade, RR (February 1985). "Liver disease and the hypothalamic pituitary gonadal axis". Seminars in Liver Disease, 5(1): 35–45. doi:10.1055/s-2008-1041756. PMID 3983651.
32. "Symptoms of cirrhosis". nhs.uk. 3 October 2018. Retrieved 22 March 2021.
33. van Thiel, DH; Gavaler, JS; Spero, JA; Egler, KM; Wright, C; Sanghvi, AT; Hasiba, U; Lewis, JH (Jan–Feb 1981). "Patterns of hypothalamic-pituitary-gonadal dysfunction in men with liver disease due to differing etiologies". Hepatology, 1(1): 39–46. doi:10.1002/hep.1840010107. PMID 6793494. S2CID 43547817.
34. Liu J., Liu Y., Mao Q., Klaassen C.D. The effects of 10 triterpenoid compounds on experimental liver injury in mice. Toxicol. Sci, 1994; 22: 34–40. doi: 10.1093/toxsci/22.1.34. [PubMed] [CrossRef] [Google Scholar].
35. Janbaz K.H., Gilani A.H. Studies on preventive and curative effects of berberine on chemical-induced hepatotoxicity in rodents. Fitoterapia, 2000; 71: 25–33. doi: 10.1016/S0367-326X(99)00098-2. [PubMed] [CrossRef] [Google Scholar]
36. Vivoli E., Cappon A., Milani S., Piombanti B., Provenzano A., Novo E., Masi A., Navari N., Narducci R., Mannaioni G., et al. NLRP3 inflammasome as a target of berberine in

experimental murine liver injury: Interference with $P2X_7$ signalling. Clin. Sci, 2016; 130: 1793–1806. doi: 10.1042/CS20160400. [PubMed] [CrossRef] [Google Scholar]
37. Donatus I.A., Sardjoko, Vermeulen N.P. Cytotoxic and cytoprotective activities of curcumin. Effects on paracetamol-induced cytotoxicity, lipid peroxidation and glutathione depletion in rat hepatocytes. Biochem. Pharmacol, 1990; 39: 1869–1875. doi: 10.1016/0006-2952(90)90603-I. [PubMed] [CrossRef] [Google Scholar]
38. Kheradpezhouh E., Panjehshahin M.R., Miri R., Javidnia K., Noorafshan A., Monabati A., Dehpour A.R. Curcumin protects rats against acetaminophen-induced hepatorenal damages and shows synergistic activity with N.-acetyl cysteine. Eur. J. Pharmacol, 2010; 628: 274–281. doi: 10.1016/j.ejphar.2009.11.027. [PubMed] [CrossRef] [Google Scholar]
39. Yousef M.I., Omar S.A., El-Guendi M.I., Abdelmegid L.A. Potential protective effects of quercetin and curcumin on paracetamol-induced histological changes, oxidative stress, impaired liver and kidney functions and haematotoxicity in rat. Food Chem. Toxicol, 2010; 48:3246–3261. doi: 10.1016/j.fct.2010.08.034. [PubMed] [CrossRef] [Google Scholar]
40. Bulku E., Stohs S.J., Cicero L., Brooks T., Halley H., Ray S.D. Curcumin exposure modulates multiple pro-apoptotic and anti-apoptotic signaling pathways to antagonize acetaminophen-induced toxicity. Curr. Neurovasc. Res, 2012; 9: 58–71. doi: 10.2174/156720212799297083. [PubMed] [CrossRef] [Google Scholar]
41. Somanawat K., Thong-Ngam D., Klaikeaw N. Curcumin attenuated paracetamol overdose induced hepatitis. World J. Gastroenterol, 2013; 19: 1962–1967. doi: 10.3748/wjg.v19.i12.1962. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
42. Li G., Chen J.B., Wang C., Xu Z., Nie H., Qin X.Y., Chen X.M., Gong Q. Curcumin protects against acetaminophen-induced apoptosis in hepatic injury. World J. Gastroenterol, 2013; 19: 7440–7446. doi: 10.3748/wjg.v19.i42.7440. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
43. Soliman M.M., Abdo Nassan M., Ismail T.A. Immunohistochemical and molecular study on the protective effect of curcumin against hepatic toxicity induced by paracetamol in Wistar rats. BMC Complement. Altern. Med, 2014; 14: 457. doi: 10.1186/1472-6882-14-457. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
44. Yao H.T., Yang Y.C., Chang C.H., Yang H.T., Yin M.C. Protective effects of (-)-epigallocatechin-3-gallate against acetaminophen-induced liver injury in rats. Biomedicine, 2015; 5: 15. doi: 10.7603/s40681-015-0015-8. [PMC free article] [PubMed] [CrossRef] [Google Scholar].
45. Wang H., Peng R.X. Sodium ferulate alleviated paracetamol-induced liver toxicity in mice. Zhongguo Yao Li Xue Bao, 1994; 15: 81–83. [PubMed] [Google Scholar].
46. Yuan J., Ge K., Mu J., Rong J., Zhang L., Wang B., Wan J., Xia G. Ferulic acid attenuated acetaminophen-induced hepatotoxicity though down-regulating the cytochrome P 2E1 and inhibiting toll-like receptor 4 signaling-mediated inflammation in mice. Am. J. Transl. Res, 2016; 8: 4205–4214. [PMC free article] [PubMed] [Google Scholar].
47. Fan Y.J., Rong Y., Li P.F., Dong W.L., Zhang D.Y., Zhang L., Cui M.J. Genistein protection against acetaminophen-induced liver injury via its potential impact on the activation of UDP-glucuronosyltransferase and antioxidant enzymes. Food Chem. Toxicol, 2013; 55: 172–181. doi: 10.1016/j.fct.2013.01.003. [PubMed] [CrossRef] [Google Scholar]
48. Hu M., Krausz K., Chen J., Ge X., Li J., Gelboin H.L., Gonzalez F.J. Identification of CYP1A2 as the main isoform for the phase I hydroxylated metabolism of genistein and a prodrug converting enzyme of methylated isoflavones. Drug Metab. Dispos, 2003; 31: 924–931. doi: 10.1124/dmd.31.7.924. [PubMed] [CrossRef] [Google Scholar]
49. Lucas A.N., Nation R.L., Milne R.W., Reynolds G.D., Evans A.M. The effects of phytoestrogenic isoflavones on the formation and disposition of paracetamol sulfate in the isolated perfused rat liver. J. Pharm. Pharmacol, 2003; 55: 639–646. doi: 10.1211/002235703765344540. [PubMed] [CrossRef] [Google Scholar]
50. Fan Y., Wei W., Luo J., Jin Y., Dai Z. Genistein promotes the metabolic transformation of acetaminophen to glucuronic acid in human L-O2, HepG2 and Hep3b cells via the Nrf2/Keap1 pathway. Food Funct, 2016; 7: 4683–4692. [PubMed] [Google Scholar]
51. Rajaraman G., Chen J., Chang T.K. Ginkgolide A contributes to the potentiation of acetaminophen toxicity by Ginkgo biloba extract in primary cultures of rat hepatocytes. Toxicol. Appl. Pharmacol, 2006; 217: 225–233. doi: 10.1016/j.taap.2006.09.005. [PubMed] [CrossRef] [Google Scholar]
52. Moon A., Kim S.H. Effect of Glycyrrhiza glabra roots and glycyrrhizin on the glucuronidation in rats. Planta Med, 1997; 63: 115–119. doi: 10.1055/s-2006-957625. [PubMed] [CrossRef] [Google Scholar].
53. Morimitsu Y., Sugihara N., Furuno K. Inhibitory effect of flavonoids on sulfo- and glucurono-conjugation of acetaminophen in rat cultured hepatocytes and liver subcellular preparations. Biol. Pharm. Bull, 2004; 27: 714–717. doi: 10.1248/bpb.27.714. [PubMed] [CrossRef] [Google Scholar].
54. Tai M., Zhang J., Song S., Miao R., Liu S., Pang Q., Wu Q., Liu C. Protective effects of luteolin against

acetaminophen-induced acute liver failure in mouse. Int. Immunopharmacol, 2015; 27: 164–170. doi: 10.1016/j.intimp.2015.05.009. [PubMed] [CrossRef] [Google Scholar]
55. Abou El-Kassem L.T., Mohammed R.S., El Souda S.S., El-Anssary A.A., Hawas U.W., Mohmoud K., Farrag A.R. Digalacturonide flavones from Egyptian Lantana camara flowers with in vitro antioxidant and in vivo hepatoprotective activities. Z. Naturforsch. C, 2012; 67: 381–390. doi: 10.1515/znc-2012-7-805. [PubMed] [CrossRef] [Google Scholar]
56. Tien Y.H., Chen B.H., Wang Hsu G.S., Lin W.T., Huang J.H., Lu Y.F. Hepatoprotective and anti-oxidant activities of Glossogyne tenuifolia against acetaminophen-induced hepatotoxicity in mice. Am. J. Chin. Med, 2014; 42: 1385–1398. doi: 10.1142/S0192415X14500876. [PubMed] [CrossRef] [Google Scholar].
57. Liu J., Liu Y., Madhu C., Klaassen C.D. Protective effects of oleanolic acid on acetaminophen-induced hepatotoxicity in mice. J. Pharmacol. Exp. Ther, 1993; 266: 1607–1613. [PubMed] [Google Scholar].
58. Liu J., Liu Y., Klaassen C.D. The effect of Chinese hepatoprotective medicines on experimental liver injury in mice. J. Ethnopharmacol, 1994; 42: 183–191. [PubMed] [Google Scholar].
59. Liu J., Liu Y., Parkinson A., Klaassen C.D. Effect of oleanolic acid on hepatic toxicant-activating and detoxifying systems in mice. J. Pharmacol. Exp. Ther, 1995; 275: 768–774. [PubMed] [Google Scholar]
60. Abdel-Zaher A.O., Abdel-Rahman M.M., Hafez M.M., Omran F.M. Role of nitric oxide and reduced glutathione in the protective effects of aminoguanidine, gadolinium chloride and oleanolic acid against acetaminophen-induced hepatic and renal damage. Toxicology, 2007; 234: 124–134. doi: 10.1016/j.tox.2007.02.014. [PubMed] [CrossRef] [Google Scholar].
61. Liu J., Wu Q., Lu Y.F., Pi J. New insights into generalized hepatoprotective effects of oleanolic acid: Key roles of metallothionein and Nrf2 induction. Biochem. Pharmacol, 2008; 76: 922–928. doi: 10.1016/j.bcp.2008.07.021. [PubMed] [CrossRef] [Google Scholar]
62. Reisman S.A., Aleksunes L.M., Klaassen C.D. Oleanolic acid activates Nrf2 and protects from acetaminophen hepatotoxicity via Nrf2-dependent and Nrf2-independent processes. Biochem. Pharmacol, 2009; 77: 1273–1282. doi: 10.1016/j.bcp.2008.12.028. [PMC free article] [PubMed] [CrossRef] [Google Scholar].
63. Honda T., Rounds B.V., Gribble G.W., Suh N., Wang Y., Sporn M.B. Design and synthesis of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, a novel and highly active inhibitor of nitric oxide production in mouse macrophages. Bioorg. Med. Chem. Lett, 1998; 8: 2711–2714. doi: 10.1016/S0960-894X(98)00479-X. [PubMed] [CrossRef] [Google Scholar].
64. Gilani A.H., Janbaz K.H., Shah B.H. Quercetin exhibits hepatoprotective activity in rats. Biochem. Soc. Trans, 1997; 25: S619. doi: 10.1042/bst025s619. [PubMed] [CrossRef] [Google Scholar].
65. Lahouel M., Boulkour S., Segueni N., Fillastre J.P. The flavonoids effect against vinblastine, cyclophosphamide and paracetamol toxicity by inhibition of lipid-peroxydation and increasing liver glutathione concentration. Pathol. Biol, 2004; 52: 314–322. doi: 10.1016/j.patbio.2004.01.001. [PubMed] [CrossRef] [Google Scholar].
66. Bousova I., Skalova L. Inhibition and induction of glutathione S-transferases by flavonoids: Possible pharmacological and toxicological consequences. Drug Metab. Rev, 2012; 44: 267–286. doi: 10.3109/03602532.2012.713969. [PubMed] [CrossRef] [Google Scholar].
67. Pang C., Shi L., Sheng Y., Zheng Z., Wei H., Wang Z., Ji L. Caffeic acid attenuated acetaminophen-induced hepatotoxicity by inhibiting ERK1/2-mediated early growth response-1 transcriptional activation. Chem. Biol. Interact, 2016; 260: 186–195. doi: 10.1016/j.cbi.2016.10.009. [PubMed] [CrossRef] [Google Scholar].
68. Ajiboye T.O. Lophirones B and C Attenuate Acetaminophen-Induced Liver Damage in Mice: Studies on Hepatic, Oxidative Stress and Inflammatory Biomarkers. J. Biochem. Mol. Toxicol, 2016; 30: 497–505. doi: 10.1002/jbt.21814. [PubMed] [CrossRef] [Google Scholar].
69. El-Shafey M.M., Abd-Allah G.M., Mohamadin A.M., Harisa G.I., Mariee A.D. Quercetin protects against acetaminophen-induced hepatorenal toxicity by reducing reactive oxygen and nitrogen species. Pathophysiology, 2015; 22: 49–55. doi: 10.1016/j.pathophys.2014.12.002. [PubMed] [CrossRef] [Google Scholar].
70. Pingili R.B., Pawar A.K., Challa S.R. Systemic exposure of Paracetamol (acetaminophen) was enhanced by quercetin and chrysin co-administration in Wistar rats and in vitro model: Risk of liver toxicity. Drug Dev. Ind. Pharm, 2015; 41: 1793–1800. doi: 10.3109/03639045.2015.1008012. [PubMed] [CrossRef] [Google Scholar].
71. Ahmed O.A., Badr-Eldin S.M., Tawfik M.K., Ahmed T.A., El-Say K.M., Badr J.M. Design and optimization of self-nanoemulsifying delivery system to enhance quercetin hepatoprotective activity in paracetamol-induced hepatotoxicity. J. Pharm. Sci, 2014; 103: 602–612. doi: 10.1002/jps.23834. [PubMed] [CrossRef] [Google Scholar]

72. Ji L.L., Sheng Y.C., Zheng Z.Y., Shi L., Wang Z.T. The involvement of p62-Keap1-Nrf2 antioxidative signaling pathway and JNK in the protection of natural flavonoid quercetin against hepatotoxicity. Free Radic. Biol. Med, 2015; 85: 12–23. doi: 10.1016/j.freeradbiomed.2015.03.035. [PubMed] [CrossRef] [Google Scholar].
73. Wojnarova L., Kutinova Canova N., Farghali H., Kucera T. Sirtuin 1 modulation in rat model of acetaminophen-induced hepatotoxicity. Physiol. Res, 2015; 64: S477. [PubMed] [Google Scholar].
74. Wang Y., Jiang Y., Fan X., Tan H., Zeng H., Chen P., Huang M., Bi H. Hepato-protective effect of resveratrol against acetaminophen-induced liver injury is associated with inhibition of CYP-mediated bioactivation and regulation of SIRT1-p53 signaling pathways. Toxicol. Lett, 2015; 236: 82–89. doi: 10.1016/j.toxlet.2015.05.001. [PubMed] [CrossRef] [Google Scholar]
75. Du K., McGill M.R., Xie Y., Bajt M.L., Jaeschke H. Resveratrol prevents protein nitration and release of endonucleases from mitochondria during acetaminophen hepatotoxicity. Food Chem. Toxicol, 2015; 81: 62–70. doi: 10.1016/j.fct.2015.04.014. [PMC free article] [PubMed] [CrossRef] [Google Scholar].
76. Masubuchi Y., Sugiyama S., Horie T. Th1/Th2 cytokine balance as a determinant of acetaminophen-induced liver injury. Chem. Biol. Interact, 2009; 179: 273–279. doi: 10.1016/j.cbi.2008.10.028. [PubMed] [CrossRef] [Google Scholar]
77. Sener G., Toklu H.Z., Sehirli A.O., Velioglu-Ogunc A., Cetinel S., Gedik N. Protective effects of resveratrol against acetaminophen-induced toxicity in mice. Hepatol. Res, 2006; 35: 62–68. doi: 10.1016/j.hepres.2006.02.005. [PubMed] [CrossRef] [Google Scholar]
78. McGill M.R., Du K., Weemhoff J.L., Jaeschke H. Critical review of resveratrol in xenobiotic-induced hepatotoxicity. Food Chem. Toxicol, 2015; 86: 309–318. doi: 10.1016/j.fct.2015.11.003. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
79. Bishayee A., Darvesh A.S., Politis T., McGory R. Resveratrol and liver disease: From bench to bedside and community. Liver Int, 2010; 30: 1103–1114. doi: 10.1111/j.1478-3231.2010.02295.x. [PubMed] [CrossRef] [Google Scholar]
80. Swanston, Jonathan (2006). "Thiophene". Ullmann's Encyclopedia of Industrial Chemistry. Weinheim: Wiley-VCH. doi:10.1002/14356007.a26_793.pub2. ISBN 3 527306730.
81. Daniel Lednicer (1999). The Organic Chemistry of Drug Synthesis. 6. New York: Wiley Interscience, 187. ISBN 0-471-24510-0.
82. Viktor Meyer (1883). "Ueber den Begleiter des Benzols im Steinkohlenteer". Berichte der Deutschen chemischen Gesellschaft, 16: 1465-1478.
83. Henry RJ (1943). "The Mode of Action of Sulfonamides". Bacteriological Reviews, 7(4): 175–262. doi:10.1128/MMBR.7.4.175-262.1943. PMC 440870. PMID 16350088.
84. "SULFONAMIDE CLASS ANTIBIOTICS". chemicalland21.com. Retrieved 17 January2014.
85. M. Madigan, J. Martinko, D. Stahl, D. Clark, Brock Biology of Microorganisms (13th ed.), Pearson Education, 2012, p. 797 ISBN 9780321735515
86. Lackie, John (2010). A Dictionary of Biomedicine. Oxford University Press, 543. ISBN 978-0199549351.
87. Wright JB. Chemistry of benzimidazoles. Chemical Reviews, 1951; 48: 397-541. DOI: 10.1021/ cr60151a002.
88. Hu, Jilan; Xue, Yu-Chuan; Xie, Mei-Yu; Zhang, Rui; Otani, Toshio; Minami, Yoshinori; Yamada, Yuji; Marunaka, Teruyoshi (1988). "A new macromolecular antitumor antibiotic, C-1027. I. Discovery, taxonomy of producing organism, fermentation and biological activity". The Journal of Antibiotics, 41(11): 1575–1579. doi:10.7164/antibiotics.41.1575. PMID 3198491.
89. Otani, Toshio; Minami, Yoshinori; Marunaka, Teruyoshi; ZHANG, Rui; Xie, Mei-Yu (1988). "A new macromolecular antitumor antibiotic, C-1027. II. Isolation and physico-chemical properties". The Journal of Antibiotics, 41(11): 1580–1585. doi:10.7164/antibiotics.41.1580. PMID 3198492.
90. Zhen, Yong-Su; Ming, Xiu-Ying; Yu, Bin; Otani, Toshio; Saito, Hitoshi; Yamada, Yuji (1989). "A new macromolecular antitumor antibiotic, C-1027. III. Antitumor activity". The Journal of Antibiotics, 42(8): 1294–1298. doi:10.7164/antibiotics.42.1294. PMID 2759910.
91. Ken-ichiro, Yoshida; Minami, Yoshinori; Azuma, Ryotaro; Saeki, Mayuko; Otani, Toshio (1993). "Structure and cycloaromatization of a novel enediyne, C-1027 chromophore". Tetrahedron Lett, 34(16): 2637–2640. doi:10.1016/S0040-4039(00)77644-1.
92. Xu YJ, Zhen YS, Goldberg IH (May 1994). "C1027 chromophore, a potent new enediyne antitumor antibiotic, induces sequence-specific double-strand DNA cleavage". Biochemistry, 33(19): 5947–54. doi:10.1021/bi00185a036. PMID 8180224.
93. "Entrez Gene: RARB retinoic acid receptor, beta".
94. Mattei MG, de Thé H, Mattei JF, Marchio A, Tiollais P, Dejean A (Oct 1988). "Assignment of the human hap retinoic acid receptor RAR beta gene to the p24 band of chromosome 3". Human Genetics. 80(2): 189–90. doi:10.1007/BF00702867. PMID 2844650. S2CID 23090420
95. Woo EJ, Marshall J, Bauly J, Chen JG, Venis M, Napier RM, et al. (2002). "Crystal structure of auxin-binding protein 1 in complex with auxin". EMBO J, 21(12): 2877–

85. doi:10.1093/emboj/cdf291. PMC 126050. PMID 12065401.
96. Hesse T, Feldwisch J, Balshusemann D, Bauw G, Puype M, Vandekerckhove J, Lobler M, Klambt D, Schell J, Palme K (September 1989). "Molecular cloning and structural analysis of a gene from Zea mays (L.) coding for a putative receptor for the plant hormone auxin". EMBO J, 8(9): 2453–61. PMC 401229. PMID 2555179.
97. Palme K, Hesse T, Campos N, Garbers C, Yanofsky MF, Schell J (February 1992). "Molecular analysis of an auxin binding protein gene located on chromosome 4 of Arabidopsis". Plant Cell, 4(2): 193–201. doi:10.1105/tpc.4.2.193. PMC 160120. PMID 1321684.