Nicotine's Impact During Metabolism in The Liver, With Disease Progression, As Well As Genetic Factors During Nicotine Metabolism

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Received August 31, 2024
Accepted August 27, 2024
Electronic access November 15, 2024

Nicotine is an addictive substance found in many conventional cigarettes and vapes. It drives the intake of many different carcinogens, several of which are known to cause cancer. Nicotine is also dangerous on its own as it can damage the liver during metabolism and affect the risk or progression of many diseases, including NAFLD (non-alcoholic fatty liver disease) and liver cancer. Nicotine can even cause mutations in the human genome. It is found naturally in many different plants, including tomatoes, but tobacco companies increase the percentage of the nicotine present, or its potency to make the cigarette more addictive. Nicotine has more negative effects beyond the liver, it can impact the heart, brain, lungs, and many other organs. This literature review paper aims to show the impact of nicotine on the hepatic system, disease progression, and genes. It also aims to convey to people just how dangerous nicotine is, to hopefully convince them to quit smoking/vaping or never to start.

Introduction

Nicotine is an addictive drug that is found in cigarettes and vapes. Beyond just being an addictive substance that triggers a person into continuing to use a nicotine product, it has negative effects on the entire body. It rewires the reward pathway by increasing the brain's resistance to dopamine and can increase the risk of getting lung cancer because when nicotine comes into contact with lung cells, it can lead to mutations in them. Using a nicotine product can also increase the chances of getting chronic obstructive pulmonary disease (COPD), strokes, or other related diseases[1].

Nicotine has several negative effects on the body, and if these effects are not studied in depth, it can have devastating consequences, including making smoking fatal. Worldwide, 35 million people use nicotine products, 8 million of which die from it every year. Around 7 million of these deaths are from direct smoking while around 1.3 million are from secondhand smoke[2,3]. Smokers and vapers (vaping is a way of intaking tobacco) are not the only ones that nicotine affects, as it can even impact people who have never smoked if they live in close quarters with people who do. Learning the effects of nicotine and smoking can educate people on why not to use these products and help eradicate one of the most avoidable causes of death in the world[4].

The hepatic system is one of the many organ systems affected by nicotine intake. This can include the liver getting inflamed due to a build-up of lipids[5]. This can eventually lead to liver failure, when the liver stops being able to metabolize, causing the hepatic system to stop functioning. This is especially bad because the hepatic system plays a crucial role in the body, processing all the food that enters and removing toxins[6]. The build-up of lipids in the caused by smoking can result in different liver diseases, including nonalcoholic fatty liver disease (NAFLD)[5]. The latter can cause the liver to inflame and impair the liver's function as a metabolizer. If left untreated, NAFLD can lead to liver failure. A study by Tamaki, et al, found that NAFLD can lead to cirrhosis, liver failure, or liver cancer[7]. Nicotine drives the repeated intake of other chemicals that can cause permanent liver scarring, also known as cirrhosis[8–11]. One study conducted by Liu et al found that there is 3 times more risk in women who smoke with liver cirrhosis[12].

Furthermore, nicotine can increase the number of cigarettes smoked through addiction, which is important because smoking is a known risk factor for liver cancer[13,14]. Smoking might also cause mutations in the human genome, especially in the liver, which increases the risk of liver cancer development[5,15]. Petrick, et al, conducted a study in which they found the relationship between tobacco usage and liver cancer[16]. They used their results to conclude that smoking cessation and decreased alcohol intake can reduce the chances of contracting HCC.

This literature review paper aims to explain the effects of nicotine on the hepatic system, and that the effects of nicotine in the body are not limited to the lungs, heart, and brain. In addition, we will cover some information about the genetic factors that cause interindividual differences in nicotine metabolism, how nicotine is metabolized, and how nicotine can affect the progression of several diseases. This literature review paper will hopefully drive people to understand better just how harmful nicotine can be and to quit smoking or vaping[4].

Nicotine Metabolism in the Liver

The variations in metabolism pathways can lead to differences in how nicotine is metabolized. Most nicotine is turned to cotinine (about 70-80%) through 5'-oxidation by the P450 2A6. The cotinine is then metabolized into either cotinine N-oxide by P450 (around 2-5% of the nicotine expelled is cotinine N-oxide), cotinine N-glucuronide by UGT2B10 (around 12-15%), trans-3'-Hydroxycotinine by UGT2B17, UGT2B7, and UGT1A9 (33-40%), 5'-hydroxycotinine (around 0.1%)[17], or norcotinine (1-2%). Some norcotinine is metabolized into hydroxynorcotinine (around 1% of the waste is this). Around 10-15% of the nicotine waste expelled remains in a cotinine form, instead of further metabolizing into the 7 substances previously mentioned. The nicotine can also be metabolized to nicotine N-oxide by FMO3 N-oxidation (around 4-7% of the waste), nicotine isomethonium ion (around 0.4-0.1%), nicotine N-glucuronide by UGT2B10 (around 3-6%), keto acid (around 1-2%) by 2'-oxidation with a middle stage of amino ketone, or nornicotine via methyl oxidation (around 1-2% of the waste). Some nornicotine is turned into norcotinine, and some may be metabolized to hydroxynorcotinine[18].

Nicotine has a multitude of negative effects on the liver while it is metabolized. It is addictive, so it drives the repeated intake of smoke, which contains numerous carcinogens. This increases the amount of toxins the liver must process, which puts immense strain on the organ. Smoking can scar your liver, which is also called cirrhosis, as well as increase the risk of developing several different liver diseases, like NAFLD[19]. Tobacco smoke contains several chemicals that are known to cause cancer. These include but are not limited to, nitrosamines, tar, vinyl chloride, and 4-aminobiphenyl[9].

Nicotine is not metabolized in the same amount in every person, as there are variations in the enzymes involved that can lead to metabolism being slow, moderate, or fast. These variations can also impact nicotine exposure and addiction risk. Instead, there are differences in the percentages of each substance in the nicotine metabolism pathway that are excreted. These changes can result from genetic or environmental factors. The genetic factors will be discussed at length later. Many environmental factors affect how nicotine is metabolized in the body. These include diet/meals (After eating a meal, the rate of nicotine metabolism increases), age (Nicotine is metabolized less effectively in the elderly), gender (Women metabolize nicotine faster on average which is related to estrogen levels in the body, as estrogen can increase the rate of nicotine metabolism), how much a person smokes (more nicotine intake increases nicotine metabolism rate), whether they are pregnant (increases rate of metabolism) if they have kidney disease (rate of metabolism and clearance goes down), and even if they are using medications (antiepileptics and adalimumab increase rate of nicotine metabolism)[17]. Kidney disease impacts the metabolism of nicotine because it can change the way nicotine is cleared from the body. Some other factors that can play a role are ethnicity (which will be further discussed in the genetic factors section and alcohol consumption (which can increase the rate at which nicotine is metabolized). Benowitz et al noted this when studying nicotine-related biomarkers, kinetics, chemistry, and metabolism. They stated in their study that nicotine metabolism is impacted by both genetic and environmental factors, with some of the environmental factors being sex, age, and diet.

Impact on Disease Progression

Nicotine is an addictive substance, so it drives the repeated intake of the many carcinogens present in tobacco or nicotine products. These carcinogens have several negative effects, although they do not always directly cause them[4]. Sometimes, they cause indirect effects by changing the progression of certain diseases or increasing the risk of getting some other diseases. In the hepatic system, there are many diseases whose progress can be altered by smoking. Smoking can also increase the risk of diseases in the hepatic system[5,9,15]. Some of these diseases include NAFLD, liver cirrhosis, and hepatitis B/C.

NAFLD (Nonalcoholic Fatty Liver Disease) is a condition in which fat and lipids build up in the liver, which damages it. NAFLD is reversible, but NASH (nonalcoholic steatohepatitis) which is a more severe type of NAFLD that can be life-threatening because it is a known risk factor for liver cancer (after cirrhosis develops), involves inflammation, liver cell damage, and the potential for fibrosis and is not reversible[20]. While NAFLD is often a silent disease[21], that does not mean that its effects are not severe. NASH causes inflammation and liver damage and can ultimately lead to cirrhosis or even liver failure[22]. Nicotine intake is a risk factor for getting NASH for a variety of reasons. First, it inactivates a protein called AMPK (adenosine monophosphate-activated protein kinase, which regulates energy homeostasis and lipid metabolism) in the intestines. The inactivation of AMPK can increase the progression of NAFLD to NASH[5,8]. Sinha-Hikim, et al, noted this in their study of the Connection of Nicotine to Diet-Induced Obesity and Nonalcoholic Fatty Liver Disease[14]. They found that nicotine can inactive AMPK, which, as stated in Figure 2's caption, can make the liver cells sensitive to nicotine. They also noted that it was possible that nicotine, as well as a high-fat diet, could lead to NAFLD. As AMPK makes cells more sensitive to nicotine, nicotine could worsen that fatty liver, eventually worsening NAFLD to NASH. However, in a study that An, et al conducted, they found that nicotine activates AMPK, not inactivates[23]. The deposits of nicotine in the body can also trigger a build-up of lipids[9] which affects the progression of NAFLD. The way nicotine triggers a build-up of lipids in the liver is related to the activation of AMPK, which stabilizes SMPD3 (sphingomyelin phosphodiesterase 3). The stabilization of SMPD3 results in the

production of lipids that accumulate in the liver. These lipids further progress NAFLD[5]. The lipids that accumulate in the liver can also inflame it.

Nicotine also impacts liver health through oxidative stress and secondary polycythemia. Secondary Polycythemia is a disease that causes the body to produce too many red blood cells. Nicotine can lead to carboxyhemoglobin, which increases red blood cell mass because of the reduced oxygen-carrying capacity. This can lead to oxidative stress in the liver[24]. Nicotine can also directly lead to oxidative stress by increasing the amount of reactive oxygen species (ROS) as well as increasing levels of free radicals. This causes oxidative stress and damages tissues and cells[25].

Smoking is also a risk factor for liver cancer because carcinogens stimulate tumor growth, suppress tumor-suppressor genes, damage DNA and cells, and cause cirrhosis, which is a known risk factor for liver cancer[26,27]. Smoking increases the risk of liver cirrhosis, a severe scarring of the liver because it increases the number of toxins that are present in the body and are processed in the liver. Murphy et al noted something like this when studying different ethnic/racial groups and how they responded to nicotine[28]. Herrera et al also stated that smoking can increase the risk of liver cirrhosis in the cohort study they conducted[29]. The increased number of toxins that the liver must process greatly increases the workload of the liver which can lead to the following: Oxidative stress, which is when the cell gets damaged due to an imbalance in free radicals and antioxidants or Liver Toxicity, which can lead to liver injury and fibrosis (tissue thickening and scarring). Thickening of the liver tissues is especially troubling because, over time, this can block blood flow to the liver[8,9]. Nicotine does not directly increase the risk of liver cancer but rather drives the repeated intake of the other carcinogens present in nicotine products. These carcinogens are toxins, which place a lot of stress on the liver[30,31]. Platel et al noted this in their study of mice with tobacco smoking[32]. They concluded that their study demonstrated that e-cigarettes on high are hazardous products when speaking in terms of genotoxicity. Some of these chemicals can damage or even change the cell's DNA. Some of these mutations may lead to cancer. In the liver, cells come in close contact with these toxins, increasing the chances of mutations, or cell damage[8]. Smoking may lead to NAFLD in nondrinkers, which is also known to be a risk factor for liver cancer[5,19].

Furthermore, smoking suppresses the immune system by inhibiting the immune system's ability to produce antibodies and can cause a loss of lymphocytes (white blood cells specialized for fighting cancer). Dahl et al reported the effects of smoking on wound healing in a clinical study. They found that wounds did not heal as efficiently, indicating that nicotine can cause a loss in lymphocytes, and may affect antibody production[33] which can lead to both innate and adaptive immunity being impaired and affects the body's ability to mount an effective immune reaction. The loss of lymphocytes makes it harder for the body to fight off cancer because T cells (a type of lymphocyte) destroy cancerous cells and natural killer cells (another lymphocyte) kills cancer tumor cells. Too few lymphocytes make it hard for the body to kill cancerous cells to stop cancer from forming. Smoking triggers tumor growth and suppresses the body's natural tumor-suppressor genes. Some of these genes suppressed include TP53 (tumor protein p53), FAT1 (FAT atypical cadherin 1), and APC (adenomatous polyposis)[34]coli. Tobacco smoke can also lead to mutations in the p53 gene, which are present in 47% of tumors from smoking[35]. Smoking can also lead to retinoblastoma protein (Rb), which regulates cell growth and division, being inhibited[36]. These are all major risk factors for developing liver cancer, a cancer that has one of the lowest survival rates[15]. (elaborate how nicotine suppresses these genes including the p53 suppression and provide insight into biological mechanisms)

Hepatitis B (also known as HBV) is a viral infection that results in the inflammation of the liver. HBV is contagious and could be either acute (severe, but it lasts less than 6 months) or chronic (lasts longer than 6 months). Most people have an acute HBV infection, but for some, it could become chronic[37–40]. If left untreated, it could lead to some serious health problems like liver damage, cirrhosis, liver cancer, liver failure, or even death[39,40]. Smoking may increase the risk of liver cancer in people diagnosed with chronic hepatitis B or C[9]. In these people, many cancer-causing chemicals in cigarettes cause further damage to liver cells, which are already at high risk of cancer because they are suffering from chronic hepatitis B/C infections[37]. Smoking can also increase necroinflammation, as well as proinflammatory cytokines production[9,37,41]. These can all make hepatitis B and C more severe[37]. Lee et al conducted a study that sought to find if there was an integration between smoking and hepatitis B/C with risk for HCC. They found that smokers with a chronic HBV or HCV infection have a higher risk of contracting HCC than people without HBV or HCV. This indicates that smoking may further the severity of HBV/HCV[42].

The diseases mentioned in this literature review are among the many diseases nicotine affects the progression of. To summarize, smoking can increase the risk of Non-alcoholic Fatty Liver Disease (NAFLD), liver cancer (especially HCC-hepatocellular carcinoma), and liver scarring (cirrhosis)[5,8,9,24,43]. It can also negatively affect the progression of fibrosis or chronic hepatitis B (HBV) or hepatitis C (HCV). Smoking can also increase the risk of death during a liver transplant[24]. In summary, nicotine, which drives the repeated action of smoking, indirectly causes numerous negative effects on several liver diseases.

Genetic Factors in Play

A person's genetics can affect how nicotine is metabolized in their liver[44]. Some alleles of a gene can change the percent-

age of the nicotine metabolized to other things, like cotinine. These differences in metabolism can also be noticed between different ethnic groups, with some types of people metabolizing nicotine to various percentages of other substances compared to other ethnic groups[44]. Genetic factors may also increase an individual's chances of getting certain diseases[45–47]. Nicotine can also cause mutations in certain genes, increasing the likelihood of developing cancer[48]. It matters that the metabolism of nicotine from person to person is different because it affects how quickly they metabolize nicotine which is related to their likelihood of addiction (people with slower nicotine metabolism are less likely to get addicted) and the effectiveness of smoking cessation aids (people with slower metabolisms respond better to cessation aids)[49]. The metabolism of nicotine also affects the risk of developing nicotine-related diseases because people with slower metabolisms smoke less, hence they intake less nicotine, so the impact on the body is less than with people with faster metabolisms. Less nicotine intake decreases the chances of developing several nicotine-related diseases, including, but not limited to, NAFLD and cirrhosis[18].

Different genotypes of the CY2PA6 (Cytochrome P450 family 2 subfamily A member 6)[50,51] gene lead to changes in nicotine metabolism. According to Yokoi et al, people with the variation *1A/*1A metabolized nicotine to around 10% N-glucuronide, around 5% to N-oxide, 1-2% into nornicotine, 13-14% into cotinine, 7% into Cotinine N-glucuronide, 22-23% into Trans-3'-hydroxycotinine, 7-8% into O-glucuronide, around 3% into Cotinine N-oxide, and around 10% remains nicotine. People with the *1A/*1B genotype metabolize nicotine into around 10% N-glucuronide, 7-8% into N-oxide, 2-3% into nornicotine, 15% into cotinine, 5% into N-glucuronide, 22-23% into Trans-3'-hydroxycotinine, 5% into O-glucuronide, around 3% into cotinine N-oxide, and 17-18% remains nicotine. The *1A/*4 genotype metabolizes nicotine into around 5% N-glucuronide, 10% into N-oxide, 2-3% into nornicotine, 25% into cotinine, 5% into cotinine N-glucuronide, 25-26% into trans-3'-hydroxycotinine, 4% into O-glucuronide, 3-4% into cotinine N-oxide, and around 10% remains nicotine. There are some differences in metabolism with the *4/*4 genotypes because only 2 people were studied. One metabolized nicotine into 40-42% N-glucuronide, 25% into N-oxide, slightly over 5% of nornicotine, cotinine, cotinine N-glucuronide, and cotinine N-oxide, and almost 20% remained nicotine. In the other person, 55% of the nicotine was excreted as nicotine, 10-13% was metabolized into N-glucuronide, 23% into N-oxide, and less than 5% of nornicotine, cotinine, cotinine N-glucuronide, and cotinine N-oxide[52,53]. Further studies are still needed to confirm this as the size of the study was very small, and the study done by Ray et al did not discuss these differences in as much detail.

There are differences in the percentages of substances that nicotine is metabolized to between different ethnic groups. In Caucasians, 48% of the nicotine is excreted as 3-HCOT, 29% as cotinine, 5.4% as Nicotine N-oxide, 5.8% as nicotine N-glucuronide, and 12% as free nicotine, on average. Meanwhile, Japanese Americans averaged around 31% of nicotine is excreted as 3-HCOT, 29% as cotinine, 10% as N-oxide, 9.7% as N-glucuronide, and 20% as free nicotine. In African Americans, 53% of the nicotine is excreted as 3-HCOT, 24% as cotinine, 7% as N-oxide, 4.2% as N-glucuronide, and 11% as free nicotine. In Latinos, 51% of the nicotine is excreted as 3-HCOT, 28% as cotinine, 5.4% as N-oxide, 6.3% as N-glucuronide, and 10% as free nicotine. In Native Hawaiians, 40% of the nicotine is excreted as 3-HCOT, 30% as cotinine, 7.4% as N-oxide, 6.7% as N-glucuronide, and 16% as free nicotine[18,54]. All these percentages are averages in that racial group, but there are still some large differences between the proportions of nicotine metabolized to different substances.

Genetic factors can increase the chances of getting some diseases. This is known as genetic predisposition, and it is because people inherit a complete set of genes from each parent, with different versions of those genes. These variations can contribute to the development of some diseases but do not directly cause them[55]. Nicotine can play a role in some of these mutations. While nicotine is not directly a mutagen, it triggers the repeated intake of tobacco smoke[56], which does contain carcinogens such as N-nitrosamines, which are known to cause DNA mutations[57]. Carcinogens cause mutations by interacting with DNA and damaging it by creating chemical bonds with the DNA molecule, which can lead to alterations in the DNA[58,59]. Cryptogenic cirrhosis is a liver disease that causes scarring of the liver without a known cause. It is believed to be caused by mutated genes that provide instructions for keratin proteins[60]. This type of cirrhosis can worsen with nicotine intake, as nicotine on its own can also lead to cirrhosis[9]. Non-alcoholic fatty liver disease is a disease in which there is a buildup of fats and lipids in the liver[61]. Some genetic factors can contribute to NAFLD, including variations in the PNPLA3 and LPL genes. Nicotine can contribute to some of the mutations mentioned[62] as well as others, that have equally harmful effects on the body. A study found that smoking one pack of cigarettes a day can cause six mutations in each liver cell every year. If enough of these mutations accumulate, it can lead to liver cancer[27]. To summarize, genetic alterations such as mutations caused by nicotine consumption can increase the chances of developing various diseases, including different cancers.

Nicotine can play a role in the alteration of a person's genome[63], some of which can occur in the liver (it was noted by Liu et al that e-cigarette can induce hepatic mutations, and e-cigarettes contain nicotine, which is a mutagen)[48,64], with some genes being more commonly mutated than others. These genes include CHRNA5 (codes for alpha 5 nicotinic receptor subunit, when mutated can lead to a higher risk of nicotine dependence), CHRNA4 (codes for alpha 4 subunit, also affects nicotine dependence), DNMT3B (this DNA variant is more common in people

of European or African ancestry, and can increase nicotine dependence, and the risk of lung cancer), and the MUC family genes (mutations in these genes are more common in smokers with lung cancer). These genes are more commonly mutated but are not the only ones mutated[63,65–67].

Nicotine has many micro effects on the body that are not easily noticed. It can increase the chances of getting some diseases by mutating the genome[48]. Genetic factors also influence nicotine, especially when considering how nicotine is metabolized (in which percentages)[44]. These differences can be noticed between groups of people of different ethnic backgrounds in the scale of a population[44]. There are also some small changes from person to person, caused by their genome[44]. In short, nicotine affects genes, and genes affect nicotine in some ways.

Methodology

This is a review paper, meaning that several scientific papers were used to make this paper. The databases used to search for these papers were Google Scholar and PubMed. Some of the filters employed include using more recent papers and using a variety of different papers, like literature reviews and original papers. Some of the keywords used include 'nicotine', 'liver cancer', 'tumor genes suppressed' and 'NAFLD progression'. To include a paper in this literature review, it had to be more recent, not more than 20 years old, it had to be relevant to nicotine and the subject I was using it for, and I avoided using Meta-Analysis or Survey based studies. The data was extracted from the papers based on how relevant it was. I used the abstract to see if the paper was related to my topic, then looked at the conclusion to see their results. I then scanned through the paper to get the main points and used that to determine if I used the paper and what topic I used the paper for.

The main points of the papers were gathered and compared against other papers. If the papers used had different results, it was mentioned in the paper. I then summarized the papers and drew conclusions from the summary. I then added in papers that were highly relevant to my topic and mentioned them in the paper. To determine the credibility of a paper, I checked to make sure it was published in a journal, and what type of journal it was published in. I avoided using blogs, which are not as credible. If I was unsure of the credibility, I read the article through and checked to make sure it had similar conclusions to research papers on the same topic. If I decided the paper was credible, I then used it in my paper, whether as a reference, or a direct mention in the paper.

Limitations, Future Directions of Paper, Literature Gap

One limitation that I encountered while writing my literature review paper was the lack of research done on the liver and the hepatic system. Most research and literature review papers done on the effects of nicotine on the body are around the lungs and the brain. The liver is rarely the first thing considered when thinking of the effects of nicotine on the human body. Some limitations that I may reach are the limitations on the research done, and the limitations of how many studies supporting other studies that have found some diseases to be linked to nicotine. Another limitation is the scope of the paper, which doesn't include several aspects of nicotine, including, but not limited to, several diseases linked to nicotine, a more in-depth look at how the immune system relates to nicotine, and which genes affect the risk of some diseases that nicotine progresses. Some future aspects of the paper could include going more in-depth on the genetic factors and what it means that there are several mutations in the liver caused by nicotine, as well as what that could lead to.

More research should be done about the long-term effects of vaping on the body, and how nicotine is metabolized differently with various genotypes to show just how harmful the substance is. There should also be more studies conducted on the effects of nicotine on the hepatic system in general, instead of just on a particular organ or in one step of metabolism, as well as the percentages of substances nicotine is metabolized to with different genotypes and the severe impact it has on the liver. There should also be more original studies done on why youth are more likely to get addicted. It's already known that teens are more likely to start because their pre-frontal cortex is still developing. But it would be interesting to see if there is a biological basis behind teens getting addicted more easily.

Discussion & Conclusion

The papers referenced in this paper agree on many things, and there are several overlaps, but not all papers reached the same conclusions. For example, An et al's study found that nicotine activates AMPK, while Sinha-Hikim et al's study stated that nicotine inactivated AMPK. Despite some conflicting viewpoints, many studies have similar findings that pair up. For example, Yokoi et al and Ray et al had similar findings on nicotine metabolism between different genotypes. Herrera et al and Murphy et al also both stated that nicotine can lead to liver cirrhosis. There were also instances where one study had a finding based off of the findings of another study. An example of this is Tamaki et al's study that found that nicotine can lead to liver cirrhosis, and Liu et al's study added on to that study to show that women have 3x more chance of developing liver scarring from consuming nicotine.

Nicotine has many effects on the body. During metabolism, nicotine deposits can build up in the liver leading to NAFLD. It also increases the number of toxins that the body has to process, which can lead to cirrhosis. Nicotine can affect the risk of getting or progressing various diseases. These include NAFLD, Liver Cirrhosis, Liver Cancer, and Hepatitis B/C. There are differences in how nicotine is metabolized, which is affected by the genome. These differences can also be noted between ethnic groups, with some groups oxidizing more nicotine than others. All in all, nicotine has many negative effects on the body.

Nicotine negatively impacts the hepatic system. It drives the further intake of many different carcinogens. These carcinogens can increase the chances of getting many diseases, or further progressing existing liver diseases. Nicotine can also mutate liver cells leading to increased chances of getting liver cancer. The strain put on the liver by smoking could also be enough to cause liver failure, or permanently damage the liver. To conclude, nicotine negatively impacts the hepatic system.

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