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NICOTINE-INDUCED TISSUE TOXICITY: ROLE OF SOLUBLE DIETARY FIBER AND ZINC OXIDE NANOPARTICLES

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ABSTRACT

With the advent of nicotine replacement therapy, the consumption of the nicotine is on the rise. Nicotine is considered to be a safer alternative of tobacco. The IARC monograph has not included nicotine as a carcinogen. However there are various studies which show otherwise. We undertook this review to specifically evaluate the effects of nicotine on the various organ systems. On the other hand, soluble dilatory fibers (SDF) and zinc oxide nano particles (ZnONP) play an important role in the management of different diseases. Based on various research evidences, the current review was also performed the effect of nicotine-induced tissue toxicity and to clarify the ameliorative effect of different SDF and ZnONP.

KEYWORDS: Nicotine, heart, liver, SDF and ZnONP.

1. INTRODUCTION

Christopher Columbus was the first person who gave information about tobacco during this voyage to the world in 1492. In between 1600, tobacco plant had unrolled in Europe, Belgium, Itally, Switzerland, Spain, France and England. Within 125 years, tobacco use was spread all over the world. In 1994, the FAD (Food and drug administration) promoted, nicotine addictive alkaloids, which content high amount in tobacco plant. Tobacco consumption has become a huge issue in India &it's implication is especially demolishing among the poor. India is 2nd largest tobacco consumer country. India has 29 states & union territories with wide cultural differences & habits; tobacco use is ingrained as a cultural practice & resultant addiction. In India, tobacco is available as smoked & smokeless (SLT) form. The number of SLT user is most in India among 120 countries. India has 152.4 million male & 80.8 million female SLT users of the world. After studying the GATS2 in 29 states, it has been noticed that more than 1/3 people has become passive smoker. In urban area, 25% people are passive smoker and the other reports of GATS2 shows, cigarettes, Khaini, Bedding, Gutkhaetc are hugely conventional tobacco products in India. Tobacco consumption makes people suffering from non-communicable diseases, premature birth. Even people are dying. As a result it has an impact on the death rate in India.

Nicotine alkaloid found in nightshade family plants (tobacco, red peppers, eggplant, tomatoes, and potatoes). It is a stimulant and powerful parasympathomimetic alkaloid. High amount nicotine found in tobacco plants. Nicotine concentration is high in smoking tobacco product than smokeless tobacco product. One cigarette (contain 1-2 gm nicotine pre 100 gm cigarette tobacco) delivers approximately10-50ng nicotine per ml plasma level. After smoking nicotine rapidly cross pulmonary membrane and primarily ionizes at 5.5 to 6 pH. Smokeless tobacco like tambacco, gutka, nicotine gum, koini, jorda etc. are containing large amount nicotine (Gori et al., 1986). After 30 minute of chewing tobacco (7.9gm) and nicotine gum (2 mg) consumption, blood nicotine concentration was increased at 15 ng/ml and 9 ng/ml respectively. In case of smokeless tobacco nicotine mainly absorb through the mucosa of oral cavity and then riches to blood stream. Then quickly moves to left ventricle of heart and way with systemic arterial circulation rich in brain. Nicotine is accumulated in gastric juice, saliva, breast milk and it easily crass blood brain barrier and placental barrier. After nicotine absorption it reached in blood stream and where pH 7.4, 69% nicotine is ionized form and 31% unionized form (Benowitz et al., 1994).70% to 80% nicotine transform in to cotinine and 4%-7% and 3%-4% nicotine converted in to nicotine N' oxide and nicotine glucuronide respectively. Nicotine N' oxide and nicotine glucuronide both are easily excreted through urine (Shigenaga et al., 1988 and Byrd et al., 1992). Nicotine rapidly metabolized then cotinine. The half-life of nicotine is 2 hours where cotinine half-life is 15 hours. Hukkanen and his group (2005) observed that averages nicotine clearance through urine about 1200 ml/min^{-1} but cotinine clearance averages about 45ml/min^{-1}.

Reactive oxygen species production, Oxidative stress, lipid peroxide increase, DNA damage etc. are the common situation produced by nicotine toxicity. Nicotine creates (through nACh receptors) various acute and long-term effects on organ systems, cell multiplication and apoptosis, throughout the body (Dani et al., 2001 and Jones et al.,1999).With respiratory exposure like irritation and burning sensation in the mouth and throat, gastrointestinal infections like excess salivation, nausea, abdominal pain, increased gastric acid secretion, vomiting, diarrhea, peptic ulcer are arrive causes of nicotine and it also promotes tumorigenesis by affecting cell proliferation, angiogenesis and apoptotic pathways (Wu & Cho. 2004).Coronary Vascular Disease, myocardial ischemia, myocardial dysfunction, myocyte necrosis, hepatic necrosis, abnormal heart rate, elevated blood pressure etc. are promoted by long term nicotine consumption (Przyklenk. 1994).

From this review work we are try to summarize the current knowledge regarding the risk of nicotine induced cardio and hepatic tissue toxicity and its preventing measure by using various type of zinc based nanoparticles and soluble dietary fibers.

2. Nicotine induced tissue toxicity

2.1. Nicotine induced cardiac toxicity

WHO reported (2015) that, approximately 17.3 to 17.5 million peoples died yearly causes CVD throughout the world. From them, 5.3 million died causes of tobacco consumption. In India society, 120 million people were tobacco addicted (Chandrupatla et al., 2017). Tobacco consumption one of the risk factors for heart diseases. It elevated hypertension, stroke, atherosclerosis, peripheral arterial disease, coronary heart disease, etc. like cardiovascular diseases. For various physiological causes, inflammation or plaque (cholesterol, platelet aggregation and other substances in the blood) buildup in the wall of arteries and blood can no longer flow properly to various parts of the body called Atherosclerosis. Nicotine consumption induced inflammation and plaque formation in arteries. Through Sirtuin (SIRT1) enzyme activation nicotine induced arterial stiffness (Ding et al., 2019).Nicotine increased catecholamine concentration in blood, result platelet aggregation in blood vessels (Flouris et al., 2009). Nicotine activated the "muscle-type" nACh receptors and promotes the proliferation of vascular smooth muscle through the TGFβ signaling pathway (Alessandra et al., 1999). The clinical resource shows that nicotine responsible for endothelial dysfunction and promotes hypertension and atherosclerosis, which is attenuated by GTP cyclohydrolase1 (GTPCH1) and de novo tetrahydrobiopterin (BH4) over expression (Jingyuan et al., 2018). Nicotine increased oxidative stress, induced fasting blood glucose level, free fatty acid and TG/HDL-cholesterol ratio. Above indicated all mechanisms are responsible for nicotine related cardiovascular diseases (Figure 1).

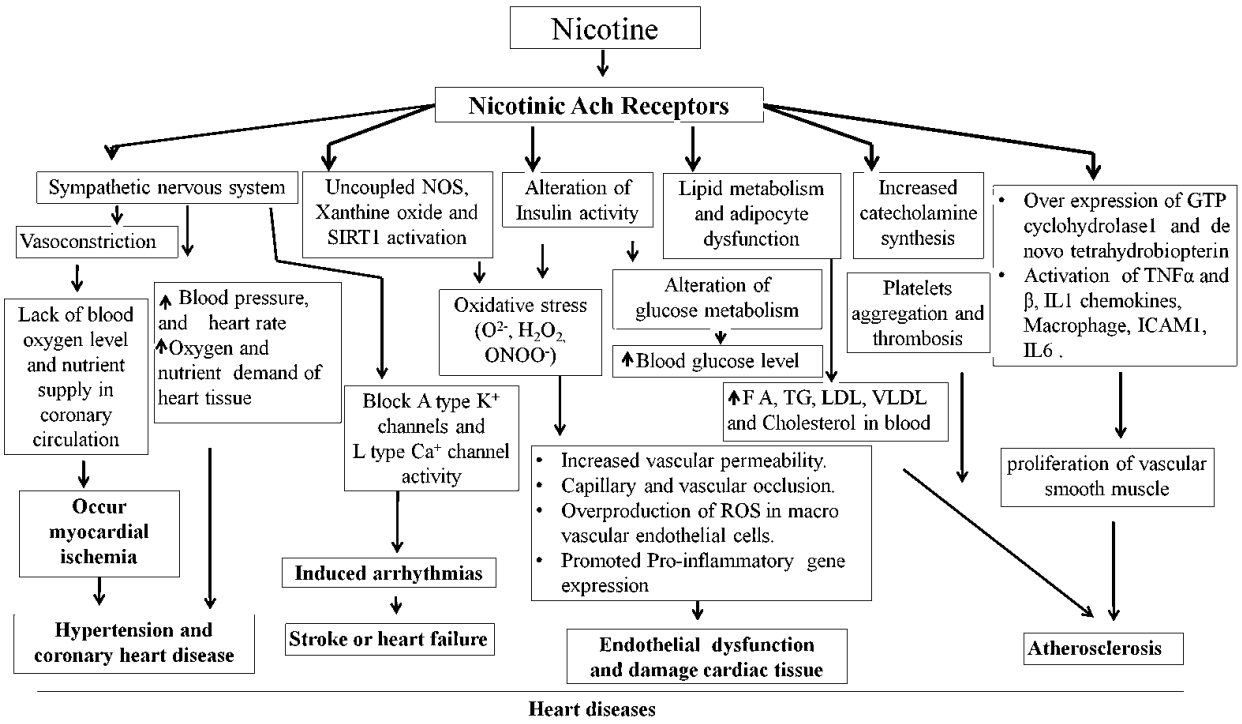

Figure 1: Pathways of nicotine induced heart diseases. FA, TG, LDL, VLDL indicate Free fatty acid, Triglyceride, Low density lipoprotein and Very low density lipoprotein respectively. NOS and ROSrepresent nitric oxide synthaseandSIRT1one type gene responsible for various diseases. ROS represent Reactive oxygen species. GTP, TNF, IL, ICAMI representGuanosine-5'-triphosphate, Tumor necrosis factor, Interleukin and Intercellular Adhesion Molecule respectively.

2.2. Nicotine induced hepatic toxicity

Liver is a popular organism for nicotine metabolism. Here large amount nicotine extensively metabolized through these liver enzymes like Cytochrome P450, aldehyde oxidase, Flavin containing Monooxygenase3, Amine n-Methyltransferase, UDP-Glucuronosyltransferases etc. (Hukkanen et al., 2005).Liver is the major organism of nicotine metabolism so it has been considered highly susceptible for the oxidative stress associated with the toxicity of nicotine. Nicotineinduced lipid peroxidation level, reduced antioxidant factors (SOD, CAT, GST, GSSH, GR etc.). Excessive ROS (reactive oxygen species) production causes of oxidative stress which induced various liver diseases, chronic and degenerative disorders (Jain et al., 2015). Not only that,nicotine altered the protein, lipid and DNA contents and modulating the pathways of normal biological functions. Causes of oxidative stress decreased liver weight, increased the mean diameter of hepatocyte and central hepatic vein. Proportionally nicotine induced mitochondrial dysfunction which responsible for elevation of liver enzymes in serum (Jensen et al., 2012) (Figure 2).

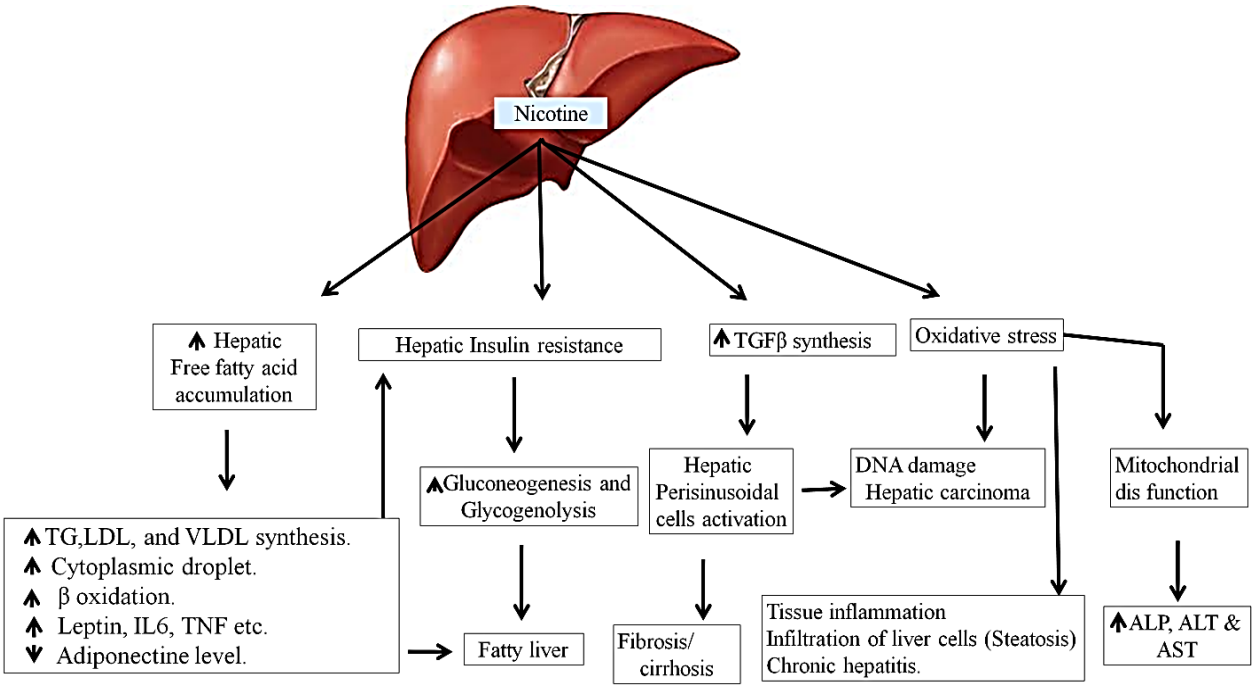

Figure 2: Mechanism of Nicotine instigatesvarious liver diseases.TGF is transforming growth factor induced cell growth and proliferation. ALT, ALP and AST are liver enzymes (Alanine transaminase, alkaline phosphatase, aspartate transaminase respectively). TG, LDL, VLDL, TNF & IL are Triglyceride, Low density lipoprotein, Very low density lipoprotein, Tumor necrosis factor and Interleukin respectively.

3. Protective effect of various SDF on cardiac and hepatic toxicity

We know that Dietary fibers are one type of non-digestible carbohydrates of plant-derived food. Plant-derived foods contain soluble and insoluble both type of fibers with significant amounts. Oat bran, barley, rice bran, nuts, seeds, some fruits, vegetables are the good sours of SDF and grain root vegetables, Fruit with edible seeds, nut, beans, purls etc. are sources of Insoluble fiber. Soluble dietary fibers (SDF) are easily dissolved in water and form gel-like substance inside the digestive system (Figure 3 and 4). Short chain fatty acids (Acetate, Butyrate, Propionate etc.) are derived formed during bacterial fermentation of non-digestible carbohydrates in intestinal gut area. We know that, Short chain fatty acids (SCFA) have a great role in our biological system. Inuline, Oligofructose, Beta-glucan, Pectin, Gums, Resistant starch, Wheat dextrin etc. are SDF. Cellulose, Chitin, Lignin etc. are insoluble fibers. In various clinical report proved that, dietary fibers supplement more effective on coronary heart disease, stroke, hypertension, diabetes, gastrointestinal disorders, obesity and cancer (Anderson et al., 2009). From a multiethnic cohort study proved that dietary fibers able to reduce the risk of fatty liver, improves hepatic metabolic conditions and it have beneficial for improve liver health (Cantero et al., 2017).

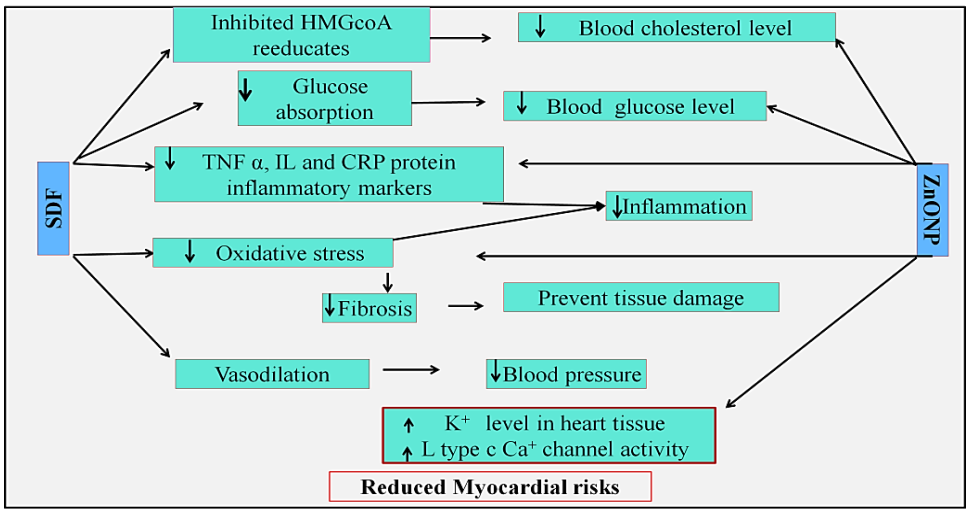

Figure 3: Therapeutic mechanism of Soluble Dietary Fiber (SDF) and Zinc oxide nano particles (ZnONPs) on myocardial risk. TNF, IL, CRP indicates Tumor necrosis factor,Interleukin and C reactive protein respectively.

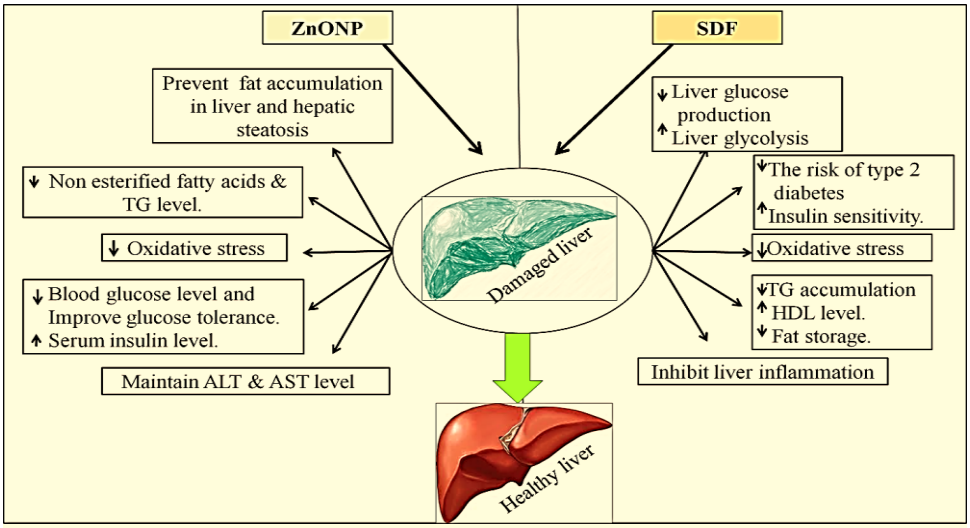

Figure 4: Mechanism of Soluble Dietary Fiber (SDF) and Zinc oxide nano particles (ZnONPs) for damage liver treatment. TNF, IL, CRP, TG indicates Tumor necrosis factor,Interleukin C reactive protein and Triglyceride respectively. ALT and AST are Alanine transaminase and aspartate transaminase.

3.1 Individual effects of functional SDFs

***Inulin and Oligofructose/Fructooligosacarids*:** Inulin one type of fructose polymers (heterogeneous blend) widely found in plant storage carbohydrates and Oligofructose is a subgroup of insulin. Whole grains, onions, garlic, leeks, Jerusalem artichoke and chicory root are good sources of them. Both are completely fermented by gut micro biota and increased bacterial population in gut.10% Inulin and Oligofructose are containing in the carbohydrate-rich diet more effectively to reduced serum triglycerides and blood cholesterol levels in hyper-cholesterolemic patients through reducing the lipogenic enzyme (mRNA) activity in the rat model. (Delzenne et al., 2002).10 to 30gm/day Inulin or Oligo fructose intake promote slower hepatic lipogenesis, modifying the hepatic metabolism, reduced body weight, improved bacterial growth and increased Magnesium, Iron and Zinc absorption (Heuvel et al., 1998).Campbell and his group (1997) reported that, in rat model 1gm Oligo fructose promoted 50 to 60 mmol/L Short chain fatty acids formation during fermentation. Inulin and Oligo fructose improve some risk factors of cardiac diseases like oxidative stress (SOD, Catalase, MDA, etc. ratio), serum cholesterol level (TG, LDL, VLDL, HDL percentage), blood sugar level and inflammation of endothelium layer. They also reduced the risk of high blood pressure and stroke (Reyes et al., 2010).

Beta-glucans: This soluble fiber construct by β-D-glucose polysaccharides where 1–3 β-glycosidic bonds present. Oats, barley, rye, wheat, mushrooms etc. are the good sours of Beta-glucans. Daily 3gm Beta-glucans consumption can reduced the probability of high cholesterol, diabetes, cancer, high blood pressure and cardiac Ischemia.92 and 131mmol/L SCFA is formed from 44gm Oats and 42gm wheatduring fermentation respectively in Pig cecum (Topping et al., 1993).

***Pectin and Gums*:** Gums are complex carbohydrate which hydrophilic type polymer containing thousands of

monosaccharide units and gums derived from cellulose. At a time gums able to n bins with large amounts water with in their branches. Pectin is one type acidic heteropolysaccharide. Pears, apples, guavas, quince, plums, citrus fruits, orange, gooseberries etc. fruits contain large amounts of pectin and cherries, grapes, and strawberries contain small amounts of pectin. Pectin present in Apples, Apricot, Cherries, Oranges, Carrots, Citrus peels at 1.5,1,0.4,3.5, 1.4 and 30 percentage respectively (Krishnamurti et al., 1948). Pectin and Gums supplements are uses for the treatment of diarrhea, constipation, irritable bowel diseases (IBS), high blood pressure, high cholesterol, weight loss and diabetes (Jones.2015).

Resistant starch: It is one type of starch that is resistant to enzymatic hydrolysis in intestine (Yongfeng. 2013).Green bananas, Beans, Peas, Lentils, Whole grains including oats and barley, Cooked and cooled rice etc. are well source of resistant starch. Smaller dose of Resistant starch (<20 gm/day for 3 weeks) can relief from hyperlipidemia, high blood sugar, increased insulin sensitivity, preventing type 2 diabetes, influence SCFA Post fermentation, decreased lipolysis and inflammation, improve gut hormone production and intestinal digestion system, prevent risk of cancer etc. (Lockyer and Nugent. 2017).

Chitosan: Chitosan is a linear polysaccharide form, obtained from crab and shrimp shells, white mushroom and chlorhexidine gluconate. Chitosan have therapeutic effect on obesity, high cholesterol, high blood pressure, and Crohn disease. Chitosan and Oligofructose combined (200 to 400mg/ kg BW/ day) effect able to reduced blood elevated cholesterol level, LDL, ALP and ASTlevel. Chitosan can individually effective on high blood cholesterol reduction(Bokura& Kobayashi. 2003).With reduction of oxidative stress it also diminished the action of pro-inflammatory factors (Tao et al., 2019).High dose (>2.4 g/day for 12 week) chitosan administration significantly decrease the elevated Diastolic Blood Pressure (Huang et al., 2018).

Short chain fatty acids (SCFAs): SCFAs are the common product produced during the fermentation of fibers through gut batteries. Approximately 500–600 mmol Short chain fatty acids are produced in the gut per day. Acetate, Propionate and Butyrate are three main types of SCFAs. Acetate, Propionate and Butyrate production ratio 60:20:20 respectively and they are absorbed by colonocytes, mainly via H^+-dependent or sodium-dependent monocarboxylate transporters (MCTs and SMCTs) (Pomare et al., 1985).SCFAs regulate glucose and lipid metabolism. It may reduce the possibility of developing gastrointestinal disorders, cancer, cardiovascular disease, reduced elevated systolic and diastolic blood pressure (Lingzhi et al., 2017, Andrade et al., 2015). SCFAs maintenance of gut and immune homeostasis decreases pro-inflammatory cytokine, reduced inflammation and it also capable to reduced oxidative stress and increased antioxidant level. It may decrease collagen deposition fibrosis and apoptosis (Vaziri et al., 2014 and Park et al., 2016). Figure 5 represent how SCFAs maintain physiological functions.

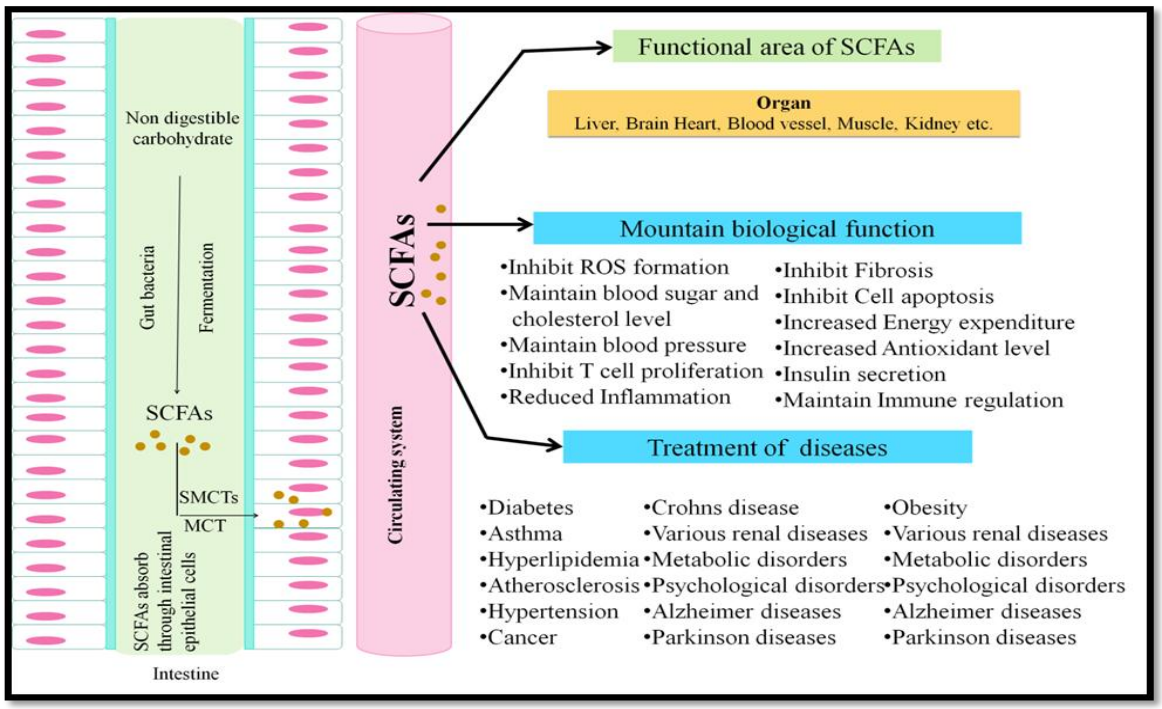

Figure 5: Formation, regulation and functions of short chain fatty acids (SCFAs). SMCTs and MCTare sodium-dependent mono-carboxylate transporters which help to transport SCFAs gut epithelial layer to circulating system.

4. Preventive role of various zinc oxide nanoparticles on cardiac and hepatic toxicity

Zinc is second abundant essential nutritionally elements in the human body. 85% zinc utilized in muscle and bone, 11% used in the liver and skin and resting part used in other tissues. In intercellularspace30 to 40% zinc is detected in nucleus and 50% located in the cytoplasm. According to recommended dietary allowance (RDA) zinc supplement assignment of women 8mg/day and 11mg/day for man. . Zinc obligates for wound healing, cell division, cell growth, breakdown of carbohydrates etc. (Zalewski et al., 2005 and Lu. et al., 2015). Zn-based nanoparticles (dimension ≤ 100 nm) have physiological important in human health. There have zinc based nano particles which are used so many physiological treatment purpose.

Zinc Oxide nano particles (ZnONP): ZnO widely used for micro and nanoparticle formation, is also increasingly being used as a material in quantum dots. ZnONPs is one of the metal oxide nanoparticles, widely used as a dietary supplement which has bioavailability, biocompatibility, and high solubility. Zinc Salt (Zinc acetate dehydrate, zinc nitrate, zinc sulfate, zinc chloride etc.) and NaOH are used for ZnONPs synthesis. Hydrothermal, Solvothermal, micro emulsion, sol-geletc. methods were applicable for ZnONPs synthesis. It has therapeutic effect on various diseases like neurological system, lymphatic system, hematological indices, sex hormones levels, fetal development, anti-inflammatory, antimicrobial activity etc. (Vizirianakis. 2011 , Jin & Jin. 2019and McNeil 2009). ZnONP could save cells from oxidative stress, decrease the levels of free radical and play a vital role against cancer(Atef et al., 2016, Mishra et al., 2017). Zinc takes part in the regulation of pancreatic beta cell function and insulin secretion. 3 mg to 300 mg/kg dose of ZnONP needed for antidiabetic effects.20nm diameter ZnONPs has anti-angiogenic activities (Divya et al., 2017).

Zinc ferrite nanoparticles (ZnFeONP): Which preparedhydrothermal method where ferric nitrate and zinc nitrate are used for formation of ZnFeONP. It has antimicrobial activity, anti-inflammatory and anticancerproperties(Anooj et al., 2017).

Zinc sulfide nanoparticles (ZnSNP): ZnSNP has higher antioxidant activities, antifungal, antibacterial property and it used in cancer therapy because ZnSNP has the ability to inhibit cancer stem cell migration. Zinc acetate or Zinc nitrate and thioacetamide are used for formation of ZnSNP synthesis (Biswas et al., 2006; Labiadh 2016 and Tran et al., 2016).

6. DISCUSSION

Tobacco addiction is deliberated a universal matter, it is well known to the public about its harmful impacts on one health and family health. Nicotine is the primary alkaloid found in tobacco plants and it is psychoactive addictive chemical. Nicotine addiction is responsible for various physiological hazards in the different organisms of human bodies. After nicotine consumption, Heart and liver are majorly affected at a time because large amount nicotine is metabolized inside of liver. Other hand nicotine affects the heart tissues by changing the heartbeat, blood pressure, and increasing tissue toxicity. In previous explanation we represent toxic effect of nicotine. SDFs have been amalgamated with the significant role in human physiological phenomenon. There have so many SDFs from them Oligfructose, Inuline and Bitaglucanare immense efficient to improved cardiac and hepatic damaged. Zinc has a great role in physiological metabolism and help to growth. But human body can't produce or store it and we must get a constant supply through our diet. Nanoparticles have useful petition in the medical field. They are very smallest probes (scale 1 to 100nm) that easily entire in biological processes. ZnONPs are the more active in medical science than other zinc based nanoparticles. ZnONPs are spontaneously synthesized by many techniques, such as green-synthesis, metallurgical, physical vapor, solvo-thermal, sol-gel, micro-emulsion chemical, hydrothermal, mechano-chemical and gaseous. It has anti-inflammatory and anti-diabetic activity. ZnONPs increased antioxidant level, reduced oxidative stress and prevent fat accumulation in liver, reduced the risk of fatty liver diseases (Vizirianakis. 2011, Jin & Jin. 2019 and McNeil 2009).Indirectly it may reduce the risk of cardiac arrest and liver diseases. Among researches proved that, ZnONPs and SDF both are able to reduced cardio and hepatic toxicity and can improved heart and liver health. Many researchers are prepared different type ZnONPs and SDF conjugation form and apply them in various physiological fields. Zinc oxide-starch Nano composite and Pectin capping ZnONPs are exhibited antibacterial activity and inhibit pathogen growth *(*Ma et al., 2016 and Moharekar et al., 2014).Chitosan-ZnO nanocomposition has anti-diatom activity *Navicula* sp. and antibacterial activity against the marine bacterium *Pseudoalteromonasnigrifaciens* (Naamani et al., 2017). Trichoderma-β-D-glucan-zinc oxide nanoparticle (T-β-D-glu-ZnO NPs) is used for cancer therapy (Kandasamy et al., 2020).

7. CONCLUSION

From the above review it may be concluded that there have so many researches established on zinc oxide nano particles and soluble dietary fibers which are beneficial for the human physiological system. There have no application of them against nicotine-induced toxicity. But they are able to protect the human body from the toxic effect of nicotine. However, our future research work will be focusing on the conjugation of zinc oxide nano particles and soluble dietary fiber against nicotinic toxicity various diseases.

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