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PROTECTIVE ROLE OF MEDICINAL PLANTS ON NICOTINE-INDUCED TISSUE TOXICITY

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ABASTRACT

Nicotine is most frequently encountered in tobacco products for smoking, chewing, sniffing and tobacco "without smoking". Nicotine is one of the most toxic of all poisons and has a rapid onset of action. Apart from local caustic actions, the target organs are the peripheral and central nervous systems. Nicotine is also a powerfully addictive drug. Burning sensation in the mouth and throat, salivation, nausea, abdominal pain, vomiting and diarrhoea. Gastrointestinal reactions are less severe but can occur even after cutaneous and respiratory exposure. A transient increase in blood pressure, followed by hypertension, bradycardia, paroxysmal atrial fibrillation, or cardiac standstill may be observed. In severe poisoning, tremor, convulsions and coma occur. Faintness, prostration, cyanosis and dyspnoea progress to collapse. Death may occur from paralysis of respiratory muscles and/or central respiratory failure. Medical plants play an important role in the management of different diseases. Based on these evidences, the current review was performed the effect of nicotine induced tissue toxicity and to clarify the ameliorative effect of different medicinal plants.

KEYWORDS: Nicotine, Lungs, Heart, Liver, Kidney, Medical Plants.

INTRODUCTION

Nicotine is a naturally occurring alkaloid found primarily in the members of solanaceous plant family, predominantly in tobacco plant (Nicotiana tabacum).[1] Also, nicotine presents lower levels in other plants such as tomato, potato, eggplant and green pepper, where nicotine acts as a natural insecticide.[2] Nicotine was first isolated and determined to be the major

constituent of tobacco in 1828.[3] In commercial tobacco, the major alkaloid is nicotine, accounting for about 95% of the total alkaloid content.[4] According to American Lung Association, cigarettes contain about 600 ingredients.[5] When they burn, they generate more than 7000 chemicals and 69 of them can cause cancer.[6] India is the second largest producer and consumer of tobacco next only to China.[7] Nicotine consumption is also hazardous to non-smokers through second- hand and third hand smoking. Referring to involuntary or passive smoking and nicotine exposure, either in private or public places, the former deteriorates health, resulting in cardiovascular diseases[8] Inhalation is the most frequent route of entry because of worldwide tobacco smoking. Nicotine is also available from smokeless tobacco (snuff, chewing tobacco), pipe and cigar tobacco, water pipe tobacco, electronic cigarettes (e-cigarettes), and a variety of smoking cessation medications. Such exposure has been reported after spilling or applying nicotine containing insecticides on the skin or clothes[9] and as a consequence of occupational contact with tobacco leaves (green tobacco sickness.[10] Nicotine absorption can occur through the oral cavity, skin, lung, urinary bladder and gastrointestinal tract. Absorption of nicotine across biological membranes depends on P^H.[11] In its ionised state, such as in acidic environments, nicotine does not rapidly cross membranes. The respiratory absorption of nicotine is 60% to 80%**.** Tobacco use is the leading cause of death in the world today. With 4.9 million tobaccos related deaths per year, no others consumer product is as dangerous or kills as many people as tobacco.[12] The most common cancers of men are lung and oral while breast and cervix cancers are common in women. A research from king's college of London found that almost 3 of 5 cancers deaths in India are associated with tobacco or infectious diseases**.**[13] Nicotine affects the heart, liver, and lead to heart attack, strokes, chronic obstructive pulmonary disease, and hypertension. The stages of these diseases in a man depend on the quantity and time period of tobacco consumption.[14] In recent days, the fact 'tobacco causes cancer' is the controversial in Indian media because of lack of awareness among people. Some people think that tobacco is not a causative agent for cancer and it does not harm human health in any ways**.**[15] Main culprit of addiction of cigarette is nicotine, which alters the balance of chemicals in a smoker's body such as dopamine and noradrenalin. When nicotine changes the levels of these chemicals, the person's mood and concentration level change and smokers find this enjoyable**.**[16] Nicotine poisoning produces nausea, vomiting, abdominal pain, diarrhoea, headache, sweating and pollor however, more severe poisoning results in dizziness, weakness and confusion, progressing to convulsion, hypotension and coma.[17]

The main aims of the present review are to summarize the current knowledge regarding the risks of nicotine-induced tissue toxicity and its preventive measured by using different medicinal plants.

Nicotine-induced tissue toxicity

A. Nicotine-induced toxicity in lungs

Exposure to tobacco smoke and nicotine during in uterus and postnatal life has been shown to disturb lung development, increase susceptibility to lower respiratory tract infections, increase prevalence of wheezing, and exacerbate respiratory symptoms in Children with chronic lung diseases.[18] Nicotine has also been shown to be concentrated in the breast milk of mothers who smoke.[19] In uteri, nicotine exposure has been reported to disrupt normal developmental processes in the lungs.[20] Long-term cigarette smoking is currently the cause of more than 90% of COPD cases in Westernized countries.[21] Lung cancer and smoking induced COPD are leading causes of morbidity and mortality worldwide. In a large longitudinal study of asymptomatic patients with mild to-moderate COPD, approximately 33% of subjects died of lung cancer over approximately 15 years, suggesting that lung cancer is a leading cause of morbidity and mortality in COPD patients.[22] Smokers with COPD also have a higher risk of developing a specific subtype of non-small cell lung cancer termed squamous cell carcinoma.[23] Passive exposure to cigarette smoke may also contribute to the development of COPD by increasing the lung total burden of inhaled particles and gases.[24] People with COPD have difficulties breathing, primarily due to the narrowing of their airways and destruction of lung tissue. Lung cancer is the leading cause of cancer death in most countries of the WHO European Region. Approximately 430 000 people died from lung cancer in the Region in 2018, and more than half a million new cases were diagnosed during that period.[25] There is now evidence that most smokers develop some respiratory impairment due to COPD.[26]

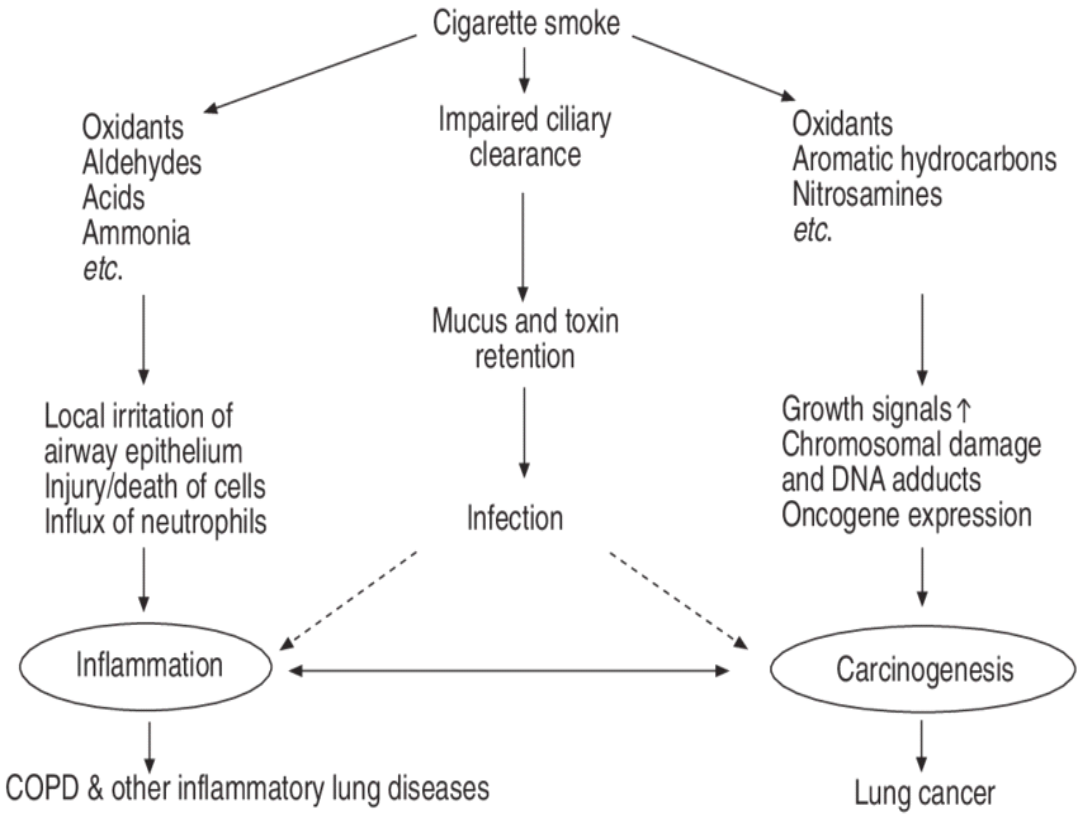

Figure 1: Mechanism of smoking induced lung diseases.

B. Nicotine-induced toxicity in heart

Consumption of nicotine is now increasing rapidly throughout the developing world and is one of the biggest threats to current and future world health.[27] It was estimated that there were 100 million deaths worldwide in the 20th century and currently, there are 5.4 million deaths every year. It has also been estimated that by 2030, there will be more than 8 million deaths every year.[28] The European Society of Cardiology reported recently that smoking causes 28% of cardiovascular deaths in men aged 35 to 69 years and 13% in women of the same age.[29] Cigarette smoking is one of the risk factors for hypertension and stroke. Smoking adversely affects the cardiovascular system in human subjects and also associated with an increased risk of atherosclerotic vascular disease, hypertension, myocardial infarction, unstable angina, sudden cardiac death, and stroke.[30]

Acute hypertensive effect was observed in smokeless tobacco users.[31] During smokeless tobacco use (5 to 30 minutes), systolic and diastolic blood pressure persistently increased. This increase remained up to 90 minutes after smokeless tobacco use. The potential long-term risk of using smokeless tobacco is obvious because smokeless tobacco induced transient hypertension may predispose smokeless tobacco users to myocardial infarction, hypertension,

and stroke.[32] Blood Pressure readings in tobacco chewers are also affected by high Na^+ content of smokeless tobacco.[33] Smoking, either active or passive, can cause cardiovascular disease, such as enhanced oxidative stress, haemodynamic and autonomic alterations, endothelial dysfunction, thrombosis, inflammation, hyperlipidaemia, or other effects.[34] Tobacco smoke, and specifically nicotine, has a significant effect on lipid metabolism and the regulation of lipid levels in the blood.[35] Cigarette smoke could promote atherosclerosis, in part, via its effects on the lipid profile.[34] Smoking is associated with significantly elevated serum concentrations of total cholesterol and triglycerides.[35] In addition, several studies have shown a tendency for low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol to be slightly higher in smokers.[36] These associations seem to be dose dependent[35] On the other hand, smoking lowers serum concentrations of high-density lipoprotein (HDL) cholesterol, a powerful protective factor against the development of atherosclerosis.[37]

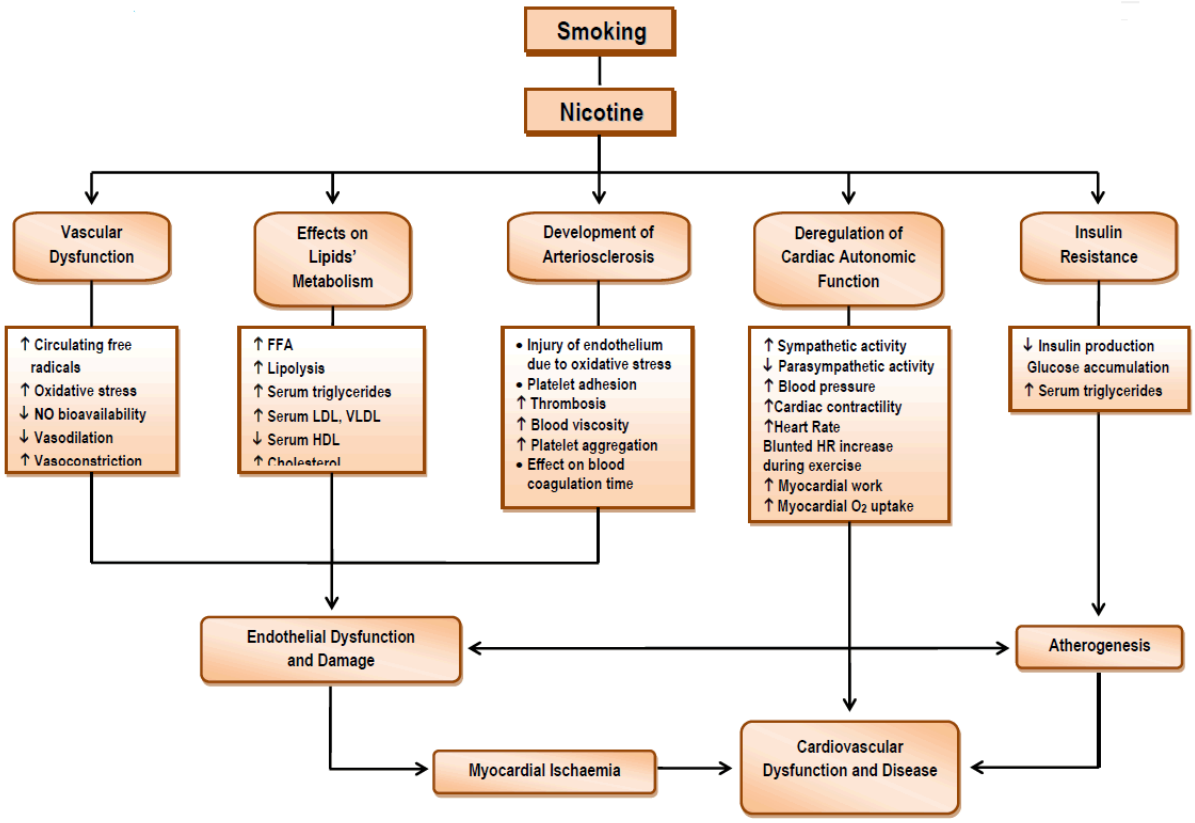

Figure 2: Mechanism of nicotine-induced Hypertension, Stroke and Atherosclerosis.

C. Nicotine-induced toxicity on liver

Nicotine, a major toxic component of cigarette smoking is rapidly absorbed through the lung and is mainly metabolized in the liver.[38] Nicotine, once absorbed, is mainly metabolized by

the liver to a number of major and minor metabolites.[11] The major metabolite is cotinine; the primary product of the C-oxidation pathway of nicotine biotransformation has been used as a marker for nicotine intake.[39] Seeing that the liver is the major site of nicotine metabolism, it has been considered highly susceptible for the oxidative stress associated with the toxicity of nicotine. In fact, many epidemiological studies have shown an association between smoking and accelerated progression of liver fibrosis in patients with a variety of chronic liver diseases such as primary biliary cirrhosis and chronic hepatitis C.[40] In an experimental study have shown that smoking caused oxidative stress and exacerbated the severity of non-alcoholic fatty liver disease in obese rats.[41] Moreover, nicotine from heavy smoking increased the risk of developing hepatocellular carcinoma.[42]

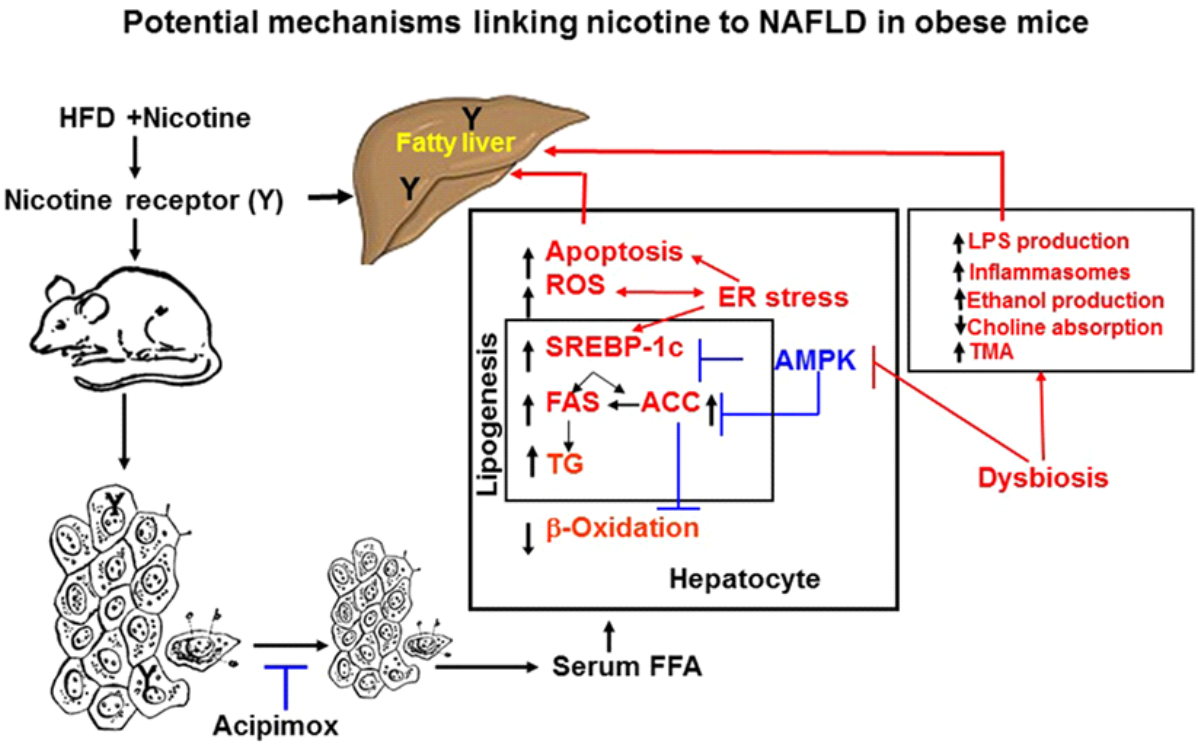

Figure 3: Mechanism of nicotine related non-alcoholic fatty liver disease.

D. Nicotine-induced toxicity in kidney

Exposure to nicotine and combustible products from cigarette smoking is toxic to renal function. There is some evidence to indicate that tobacco chewing and smoking increases the risk of renal function impairment in general population.[43] Micro proteinuria (Micro albuminuria) is defined as, small quantity of protein excreted in urine per day. It is an early indicator for the progressive kidney damage.[44] Micro albuminuria may be due to various pathophysiological, mechanisms in tobacco chewers and smokers. Earlier studies remarked

that nephropathies are accelerated by nicotine with an increased incidence of micro albuminuria progressing to proteinuria, followed by type-1 diabetes mellitus induced renal failure.[45] Tobacco chewing and smoking induces renal damage may be through enhancing the synthesis of free radicals may lead to alter the glomerular function leading to elevate the levels of urea and creatinine in tobacco chewers and smokers.[46] Tobacco chewing and smoking may also be responsible to decrease in renal plasma flow and glomerular filtration rate. It is well known that urinary albumin is a responsive marker of glomerular injury and there is a relationship between tobacco chewing and smoking with albuminuria indicates direct or indirect renal damage induced by tobacco chewing or smoking.[47] Cigarette smoke, particularly nicotine and its metabolites cause cancers of the bladder and kidney.[48] Nicotine encourages renal vasoconstriction in healthy non-smokers possibly through alteration of a cyclic-GMP-dependent vasoactive mechanism.[49] Cigarette smoking (nicotine) is also associated with augmented progression of nephropathies responsible for end stage renal disease.[50] Patients are predisposed to urinary tract cancers. Associated with altered renal function is a direct effect on nervous innervations, blood pressure and blood.[51]

Role of different medicinal plants on nicotine-induced tissue toxicity

A. Role of *emblica ofiicinalis* (Amla)

Emblica officinalis is a euphorbiaceous plant, widely distributed in subtropical and tropical areas in India. It has abundant amounts of vitamin C and superoxide and is used in many traditional medicinal systems. Emblica fruit is reported to have hypolipidemic[52], hypoglycaemic[53] activities and also acts as an important constituent of many hepatoprotective formulations available.[54] It is also used as antimicrobial,[55] anticancer[56] and anti-inflammatory agent.[57] It was reported that emblica has a strong antioxidant activity,[58] which may be partially due to the existence of flavonoids and several gallic acid derivatives including epigallocatachingallate.[59] Phytochemical compound are present in the natural products (Amla) in reducing or detoxifying the effect of nicotine. *Emblica officinalis* is rich in vitamin C and serves as good antioxidant.[60] The antioxidant properties of *Emblica officinalis* extract are many times more than that of water soluble vitamin E.[61] It was reported that *Emblica officinalis* serves as an effective scavenger of free radicals, which helps to protect the nicotine induced toxicity in rats, both biochemically in restoring the enzymes level and also helping/repairing the damages hepatocytes.[62]

B. Role of *azadirachta indica* (Neem)

Neem (*Azadirachta indica*) belonging to the family, Meliaceae is an evergreen tree, cultivated in various parts of the Indian subcontinent.[63] The neem leaf has been reported to exhibit various pharmacological activities, including anti-inflammatory[64] , antioxidant[65], antimicrobial[66] and antiviral properties.[67] Active constituents of the neem leaf include nimbi, nimbidine, isomeldenin, β-sitosterol and quercetin.[68] It has been reported to protect against endotoxemia in mice exposed to lipopolysaccharide (LPS).[69] NLE (Neem Leaf Extract) attenuates the production of ROS. A previous study shows that, treatment with NLE significantly decreased the levels of ROS. NLE decreases the levels of TNF-α and IL-6 in BALF but increased release of TNF-α and IL-6 is one of the major characteristics of COPD.[70]

C. Role of *allium sativum* (Garlic)

Garlic (*Allium sativum*, Linn) is a condiment, which for several years has been used in India for its medicinal purposes. It has been used for conditions like, fever, cough, digestive disorders and respiratory diseases like pulmonary tuberculosis.[71] Administration of nicotine (1mg/kg) to the animals also raised the serum cholesterol, triglycerides and glucose levels. This is consistent with the reports of Schienalbein (1982) that nicotine causes the elevation of plasma free fatty acids which may serve as building blocks for the synthesis of both cholesterol and triglycerides.[3] The crude extract of garlic caused a decrease in the levels of cholesterol, TG and glucose. This result is also consistent with the finding of Bobboi et al., (1984).[72] It is plausible to suggest that, the unsaturated side chains of garlic oil might have oxidized the reduced pyridine nucleotide which are necessary for fatty acid synthesis or might have inactive thiol groupings.[73,74] A Study was shown that crude garlic extract has the potential of significantly lowering the blood cholesterol, triglycerides and glucose levels of near normal levels in nicotine treated rats.[75]

D. Role of *curcuma longa* (Turmeric)

Nicotine induced the increased production of cAMP in blood. Increased cAMP in blood stimulates gluconeogenesis and glycogenolysis[76] as a result of which the blood glucose level is increased. It have been shown that the curcumin possesses anti-diabetic property which is partly due to a reduction in hepatic glucose production caused by activation of AMP kinase and inhibition of G6P-ase activity and PEPCK activity.[77] Nicotine stimulates catecholamine synthesis which lipolysis adipose tissue, resulting an increment in the level of triglyceride.[78]

Curcumin showed an obvious hypocholesteromic effect that could be due to an effect on total cholesterol absorption[79] and degradation or elimination.[80] Curcumin abrogated the harmful effect of nicotine on reproductive organs weight.[81]

E. Role of *camellia sinensis* (Green Tea)

Green tea (Camellia sinensis), a commonly used beverage, contains appreciable amounts of phytochemicals especially poly phenols.[82] The dried leaves of green tea havebeen reported to contain 10-25% polyphenols including flavonols and flavonoids. The main components of the green tea polyphenolic catechins are epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate (ECG), epicatechin (EC) and epigallocatechin (EGC). The epigallocatechin-3-gallate (EGCG) is the main catechin in green tea and is an effective antioxidant with potent radical scavenging abilities.[83]

Blood glucose levels increased of both male and female new-born mice in response to nicotine but green tea supplementation improved blood glucose levels in nicotine-exposed both male and female new-born mice. Similarly, green tea extract supplementation markedly decreased blood glucose levels in nicotine-exposed. Supplementation of green tea extract improved serum cholesterol levels in nicotine-exposed male new-borns Nicotine-exposed female new-borns supplemented with green tea showed significantly ameliorated serum cholesterol levels.[84]

CONCLUSION

In the above review it may be concluded that plant is safe at its proper therapeutic use. But modern society has lack of knowledge about proper uses of different herbal medicinal plant against nicotine induced toxicity. Amla, Neem, Garlic, Turmeric and Green Tea all are active herbal medicinal plant and they can easily control different nicotine-induced toxicity on lungs, heart, liver and kidney. Many researchers have been already done and more remain to be done on their safe and effective use.

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