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Review Article

# Effects of cigarette smoking on the response of hypertensive patients to beta-adrenergic antagonists: a narrative review

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## Abstract

Cigarette smoking is one of the hypertension risk factors which can adversely affect the quality of life. This review aimed to provide a brief overview of the link between smoking and hypertension. At the same time, raising questions about how smoking interacts with beta-adrenergic antagonists that are used as antihypertensive drugs. By searching for relevant studies through multiple search engines, there is inconsistent evidence about the effect of smoking on high blood pressure. Mainly attributed to the availability of numerous confounding factors. However, cigarette smoking cannot be ignored because smoking exerts dual effects on hypertension as a disease and the treatment with antihypertensive drugs, particularly beta-adrenergic antagonists. The potential drug interaction can occur through pharmacokinetics and pharmacodynamics mechanisms resulting in influencing the efficacy of these drugs. It is necessary to have dosage modifications according to the patient's smoking status, whether in hospitals or outpatient clinics.

**Keywords:** Cigarette Smoking, Beta-Adrenergic Antagonists, Hypertension, Drug Response, Iraq

## Background

According to the World Health Organization (WHO), the tobacco epidemic is one of public health's most significant threats. It is responsible for more than 8 million deaths annually [1]. Globally, the major tobacco users live in low- and middle-income countries (LMICs), whereas slowly but regularly decreased usage is reported in several high-income countries [1,2]. However, there is a trend toward reducing tobacco use due to efforts made by different countries to apply tobacco control measures [3]. In general, cigarette smoking is considered to be the most common form of tobacco use [1]. Economically, tobacco use burdens the healthcare system, rendering the strategy of smoking cessation a highly cost-effective way to decrease tobacco-related morbidity and mortality [1–3]. Non-smokers can also be exposed (passive smoking) to the harmful effects of smoking on health [4]. Passive smoking or second-hand (involuntary smoking) is when people breathe in the smoke released from a cigarette's burning end or other tobacco products, such as bidis and water pipes, and the smoke that the smoker exhales [1,4]. Exposure to passive smoking is responsible for about 1.2 million deaths annually [1]. The cardiovascular system is one of the critical smoking-target organs [5], where the damage to the heart and blood vessels can be precipitated by either active or passive smoking [5,6]. Although, it is unclear whether cigarette smoking has a long-term impact on blood pressure and the occurrence of hypertension [7]. There is no doubt that among cardiovascular parameters, tobacco smoke adversely impacts blood pressure [5]. Furthermore, the interaction of cigarette smoking with antihypertensive drugs affects hypertensive patients' management, thus achieving the required therapeutic response [5,8]. This review aimed to provide a concise overview of the association between cigarette smoking and hypertension. Also emphasized the potential interaction between smoking and beta-adrenergic antagonists used as antihypertensive drugs.

## Methods

We searched relevant studies through several available databases, including Medline, PubMed, and Google Scholar. The related studies have undergone a carefully review to obtain all pertinent information.

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## An overview of hypertension

According to the WHO guidelines, hypertension, as well-known as high blood pressure, is defined based on specific systolic or diastolic blood pressure or rein accordance with the reported use of antihypertensive medications [9]. At the same time, the International Society of Hypertension (ISH) stated a more precise definition of hypertension as an office blood pressure reading of more than 140/90 mmHg [10]. Based on the evidence, hypertension is considered a severe medical condition that causes a significant rise in the risk of heart, brain, kidneys, and other organ diseases [11]. Over the past four decades, the global mean blood pressure of the population has remained constant or has been slightly reduced through the widespread use of antihypertensive medications [7]. About 1.28 billion adults between 30 and 79 years have hypertension, mostly about two-thirds within LMIC; however, only 14.0% of conditions are under control [9,11]. The regional diversity in hypertension prevalence can be attributed to the differences in the efficacy of healthcare services provided among different countries [7]. In addition, variations exist in hypertension risk factors such as obesity, physical inactivity, alcohol use, tobacco consumption, and unhealthy diet [7,9].

## Evidence-based association of hypertension with cigarette smoking

Cigarette smoking impacts the risk and incidence of hypertension, causing a decrease in life expectancy and harmfully affecting the quality of life [12]. LMICs are particularly concerned because the continuous increase in smoking behavior will increase the burden of health care for high blood pressure [13]. The results were still paradoxical based on recent data on the relationship between cigarette smoking and elevated blood pressure [14–17]. The possible reasons for such a discrepancy among studies can be attributed to the long-term and cumulative effects of current smoking on health which may not result immediately in deleterious conditions [12]. Therefore, current smoking cannot, in common, be a direct indicator of chronic diseases initiated slowly [12]. There is either a dose-response association between smoking and a high risk of hypertension or an absence of such an association [16]. Has been reported a weak positive relation between cigarette smoking and the risk of hypertension based on multiple prospective cohort studies [7]. The direct influence of cigarette smoking on hypertension cannot be sufficiently established because elevated blood pressure cannot be lowered by cessation of chronic smoking [7,18,19]. The role of smoking cessation programs regarding blood pressure remains uncertain [17]. As stated by Li et al. [20], smoking cessation significantly decreases the risk of hypertension, and current smoking is not a risk factor for hypertension. There is a direct relationship between the duration of smoking and the occurrence of high blood pressure, even with quitting smoking, which highlights the constant harmful effect of smoking cigarettes. [19]. Similarly, the study by Zhang et al. [16] reported that cumulative exposure to cigarette smoking was related to increased systolic blood pressure in the Chinese population, particularly the minority population. In contrast, another study illustrates that smoking is one of the prime preventable causes of hypertension, a condition that can be controlled to a large extent by smoking cessation [12]. Whereby conducting a smoking cessation program, there was a significant improvement in systolic and diastolic blood pressure [17]. Several confounding factors related to the lifestyle, diet, physical activity, and socioeconomic characteristics of individuals can affect the link between cigarette smoking and hypertension [15,21]. Wang et al. [14] and Lan et al. [15] report the absence of an association between cigarette smoking and high blood pressure. Attributing the result to the existence of several confounding factors, such as alcohol consumption [14]. Both cigarette smoking and alcohol consumption often occur synchronously. They are frequently associated with weak blood pressure control in males [14,19]. The males vs. females tend to be more smokers and alcohol consumers [19]. The variation in alcohol consumption and the metabolism patterns between males and females resulted in regular alcohol consumption on blood pressure levels [14]. The proposed mechanism suggests that the neurochemical action of nicotine and alcohol is commonly enhanced [14].

In contrast, nicotinic acetylcholine receptors (nAChRs) influence alcohol consumption behaviors [14]. In addition to the effective treatment with antihypertensive drugs, it is necessary to intervene at the public health level to decrease the burden of cigarette smoking and alcohol consumption on blood pressure [14]. Moreover, the overestimation of the relationship between smoking and blood pressure can be due to poor adherence to the used antihypertension medications [16]. Female smokers have lower blood pressure, which is attributed to several factors, such as the physiological effects of daily cigarette smoking and the usual lifestyle, like diet and physical activity [15]. However, older females report a sharp increase in their systolic blood pressure compared to males [13], which might be related to hormonal changes during menopause [13]. Therefore, an individual's age can confound the effect of smoking on blood pressure [16]. The aging process, rather than the cumulative effect of tobacco smoke, can further contribute to deteriorating health conditions [16].

A high body mass index is associated with elevated blood pressure because of the contributory effect of high adiposity levels [21]. Thus, the lower body mass index induced by cigarette smoking makes lower blood pressure observed in smokers vs. non-smokers [13,16,21]. Furthermore, the psychological status of individuals also plays a role [13]. Where smokers' individuals express themselves to be calmer and less stressed, and upon smoking cessation, there is an increase in their stress level [13]. Because of the temporary excitement of smoking, smokers have an optimistic self-estimation of their health status. Therefore, as smoking is continued, there is further masking of the early warning symptoms of some diseases [12]. Furthermore, the reported current smoking status in the literature may not effectively reflect the consumption and may be closely uncorrelated with the current health status of participants [12]. Substantial evidence is present about the harmful effects of cigarette smoking on the health of children and teenagers [22]. Hypertension is reported in about 1% to 3% of children, where 80% of cases can occur because of several contributory factors [22]. These factors include socioeconomic and nutritional status, family history, body mass index, and smoking [22]. However, the effect of cigarette smoking remains unclear [22,23]. Aryanpur et al. [22] conducted a meta-analysis of epidemiologic studies. The results revealed the absence of an

association between smoking, whether active or passive smoking and the development of hypertension in children and adolescents. However, they reported increased systolic blood pressure levels because of passive smoking [22]. Based on a cross-sectional study of US children and adolescents' sample, Levy et al. [23] suggest that exposure to tobacco smoke is related to high blood pressure. Such finding demands particular attention at earlier ages to avoid further health complications at later ages [23]. It is plausible that reducing young people's exposure to tobacco smoke can reduce economic costs and protect people from high blood pressure and cardiovascular diseases in the future [23].

## Cigarette smoking and the cardiovascular system

Many chemical compounds of smoking, comprising more than 9000 entities, are generally concentrated and condensed in any tobacco mixture [5,24]. Six of these compounds are responsible for structural and functional changes in the heart and blood vessels [5,24]. These compounds are mainly nicotine and carbon monoxide, oxidizing chemicals, volatile organic compounds, particulates, and heavy metals [6,24]. However, the effects vary depending on several factors associated with the type of smoking, the environment, and the exposed subject [5]. In general, the primary mechanisms of smoking-inducing cardiovascular disease are oxidative injury, endothelial damage and dysfunction, enhanced thrombosis, chronic inflammation, hemodynamic stress, adverse effects on blood lipids, insulin resistance and diabetes, decreased oxygen delivery by red blood cells and arrhythmogenesis with a potential increase in angiogenesis [6,18,24].

Nicotine and carbon monoxide exert toxic effects on the heart and blood vessels through different mechanisms [6]. Nicotine is the primary active component of tobacco smoke [25]. Its main systemic hemodynamic effect is acute stimulation of the sympathetic nervous system resulting in increased release of norepinephrine from adrenergic neurons and epinephrine from the adrenal gland and vascular nerve endings [6,18,24,25]. These effects are mediated by stimulating the central and peripheral nervous system's nicotinic cholinergic receptors [24]. Benowitz and Burbank [24] reported that when the plasma epinephrine increased by more than 150% by cigarette smoking, the acute rise of cardiac work may result. Mostly in terms of increased heart rate, myocardial contractility, and blood pressure stimulation, regardless of administering nicotine or tobacco smoke [24]. The evoked responses are originally transient but become repeatable as they are maintained by catecholamine release [6]. Nicotine from cigarette smoking can also contribute to the pathophysiology of hypertension by causing direct endothelial damage [20]. The consequences are endothelial dysfunction, impairment of endothelium-dependent coronary vasodilation, and decreased nitric oxide production [6,20,24]. Endothelial dysfunction usually occurs in active and passive cigarette smokers [24]. The main effects of carbon monoxide are removing oxygen from oxyhemoglobin, increasing carboxyhemoglobin concentrations, and causing tissue hypoxia [6]. Because of carbon monoxide, the resultant hypoxemia can worsen preexisting conditions such as angina pectoris and congestive heart failure [24]. Also, it contributes to smoking-related thrombogenesis by raising blood viscosity because of body compensation through increasing red blood cell mass [24]. The effects of nicotine and carbon monoxide on the heart and blood vessels help explain the damage seen in smokers or even in passive smokers [6]. Acute exposure to cigarette smoke usually starts as a functional one but transiently affects the endothelium and myocardium [6]. It is identified among passive smokers who are either healthy non-smokers or those who suffer from ischemic heart disease [6].

## Management of hypertension under the influence of cigarette smoking

The initiation of pharmacological treatment of hypertension is mainly considered when lifestyle modifications are ineffective in managing high blood pressure [10]. These lifestyle modifications involve smoking cessation, regular exercise, salt intake reduction, weight loss, alcohol restriction with a healthy diet, and drink intake [26]. Like non-smoker hypertensive patients, smoker patients, specifically elderly heavy smokers, use antihypertensive drugs to control their hypertension [5]. When smoker hypertensive patients are treated, their response to antihypertensive drugs is typically affected [5]. The response of antihypertensive medications in smokers is either highly reduced, as seen mainly with beta-adrenergic antagonists, angiotensin-converting enzyme inhibitors, and diuretics, or moderately reduced, as with calcium channel blockers [5]. The response of angiotensin receptor blockers drugs to smoking is not yet established [5].

## Modulation of pharmacological effects of beta-adrenergic antagonists under the influence of cigarette smoking

Among the main classes of antihypertensive drugs, beta-adrenergic antagonists appear primarily affected by the adverse effects of smoking [5]. According to the WHO and ISH guidelines, beta-adrenergic antagonists are mainly considered for hypertensive patients with cardiac conditions, like ischemic heart disease or heart failure [10]. Once beta-antagonists bind to the beta-1 and beta-2 receptors, they inhibit effects mediated by binding epinephrine and norepinephrine to these receptors [27]. Therefore, beta-antagonists can primarily reduce blood pressure by decreasing cardiac output and inhibiting renin release from the kidney, blocking the activity of beta-1 adrenoreceptors in the heart and kidney, respectively [27,28]. Beta-antagonists also exhibit adverse chronotropic and inotropic effects on the heart [27,28]. These drugs can treat other conditions such as hyperthyroidism, essential tremor, glaucoma, and migraine prophylaxis [28]. Beta-antagonists can be classified as non-selective agents; they bind to and induce antagonizing effects via beta-1 and beta-2 receptors, such as propranolol (a prototype of beta-antagonists), carvedilol, sotalol, and labetalol [27,28]. In contrast, the cardio-selective beta-antagonists can only bind to the beta-1 receptor, such as atenolol, bisoprolol, metoprolol, and esmolol [28]. Beta-antagonists have additional alpha-1 receptor activity such as carvedilol and labetalol [28]. Thus, they have a more distinct clinical effect on treating hypertension [27,28].

The interaction between smoking compounds and beta-antagonists affects the action and efficacy of these drugs through pharmacokinetic and pharmacodynamic interaction mechanisms [8,29]. Beta-antagonists are less effective in managing smokers' high blood pressure and heart rate reduction than non-smokers [5,25]. In contrast, it was found that there were no differences between smokers and non-smokers in

clinical trials regarding the use of beta-antagonists for the primary prevention of myocardial infarction in hypertensive patients [25]. Drug interaction is defined as interference of a patient's response to a particular drug by co-administered drugs, dietary supplements, formulation excipients, disease, and environmental factors such as smoking [29,30]. It is essential to review the current smoking status of hypertensive patients to avoid an additional risk that may occur due to potential drug interactions with smoking [29,31], where it is possible to prevent any harm to patients because of a drug interaction [30]. The harmful effect can occur because increasing drug effects lead to toxicity or reduces the drug's effect, leading to therapeutic failure [30].

## Influence of cigarette smoking on the pharmacokinetic characteristics of drugs

The principles of pharmacokinetics include absorption, distribution, metabolism, and elimination of drugs, meaning "what the body does to the drug" [8,30]. Chemical compounds of smoking are responsible for pharmacokinetic interactions through the activity of cytochrome (CYP) P450 enzymes [29,31,32]. These enzymes are responsible for the metabolism of drugs and the detoxification of xenobiotics [33]. The interaction with CYP enzymes is mediated primarily by polycyclic aromatic hydrocarbons (PAHs) of tobacco smoke [29,34]. The PAHs compounds are products of the incomplete combustion of tobacco. They are considered some of the leading lung cancer-causing substances in tobacco smoke, also known as drug-metabolizing enzyme inducers [25,31,32]. Mainly, PAHs induce the activity of CYP1A1, 1A2 isoenzymes located in the liver, small intestine, and lung tissues, CYP 2B6 and possibly, CYP2E1 isoenzymes [29,32,35].

Among beta-antagonists, two drugs are the major substrates of CYP1A2 enzymes, which are betaxolol (beta-1 selective adrenergic receptor blocking agent) and propranolol (a non-selective beta-adrenergic receptor blocking agent) [34]. CYP1A2 enzymes significantly metabolize these drugs, and by inducing these enzymes, the therapeutic efficacy is reduced because of decreasing the plasma concentration of substrate drugs [31,34]. The major substrate drugs are more likely affected by changes in smoking status compared to minor substrate drugs such as carvedilol which possess beta- and alpha-adrenergic blocking activity [34].

Several factors exist, leading to individual variation in pharmacokinetic drug interactions [34]. Particularly for genetic polymorphisms of the CYP1A2 gene and the apparent racial differences in the distribution of CYP1A2 mutations [29]. Moreover, the bioavailability of the components of cigarette smoke and the extent of inhalation affects enzyme induction [29]. Where the induction of CYP1A2 activity by smoking occurs in a dose-dependent manner, smoking 1 to 5 cigarettes per day raises the activity of the CYP1A2 enzyme by about 1.2-fold [35]. Consumption of more than ten cigarettes per day is associated with maximum induction of CYP1A2 activity, about 1.7-fold [35]. It is still being determined whether or not the amount of cigarette smoking or the existence of inter-individual variations can impact CYP1A2 induction [29,34].

Nevertheless, the evidence appears that in heavy smokers (more than 20 cigarettes/day) compared to light smokers, the activity of CYP1A2 is significantly high enough to result in a tremendous rise in the induction of drug metabolism and, ultimately, the clearance of drugs [29,34]. Co-administered other medicines can also impact the risk of CYP1A2 drug interactions [34] as several drugs and substances can also induce the CYP1A2 enzymes, such as char-grilled food, rifampin, carbamazepine, omeprazole, phenobarbital, and primidone [34,35].

Among PAHs compounds, mainly 3-methyl- phenanthrene can induce other metabolic enzymes, which are uridine diphosphate (UDP)-glucuronosyltransferases (UGT) that are located primarily in the liver and catalyze glucuronidation reactions [25,31,36]. Glucuronidation is a detoxifying mechanism that changes the physiological and pharmacological activities of chemicals within the body, making them have fewer biological activities [36]. Numerous endogenous and exogenous compounds undergo glucuronidation, such as bilirubin, steroid hormones, fat-soluble vitamins, environmental toxins, and many medications [36]. Multiple factors are responsible for the marked inter-individual variations in glucuronidation rates, such as age, disease, and xenobiotic exposure, which possibly can affect the capacity for drug metabolism [36]. Smoking via PAHs can induce the glucuronidation of propranolol, carried out by UGT1A9, UGT2B4, and UGT2B7 enzymes in the liver UGT1A10 enzyme, which exists extrahepatically [25,37]. As a result, it was reported that after administering a single dose of propranolol, the area under the curve was about 50.0% lower in smokers vs. non-smokers [25].

In contrast, oral clearance increased by about 77.0% [25]. Most probably due to the dual effect on metabolic pathways of propranolol by increasing side-chain oxidation, which is catalyzed principally by CYP1A2 and, to some extent, by CYP2D6 [25,37]. Also, changes in drug clearance might occur through the induction of glucuronidation, with no apparent effect on the ring oxidation metabolic pathway of propranolol [25,37]. No changes were reported in half-lives of propranolol between smokers and non-smokers, which means that the increase in oral clearance occurs because of an increase in first-pass metabolism [25,33]. Other smoking compounds may also contribute to the interaction with hepatic enzymes but have fewer significant effects, such as acetone, pyridine, heavy metals, benzene, carbon monoxide, and nicotine [31].

It is essential to monitor patients' smoking status in a clinical setting [29,34], considering dosage modifications for smoker patients, particularly heavy smokers or those who start smoking [31,34]. However, the dose of propranolol, for example, may need to be increased to achieve the required therapeutic response [8,29]. Those exposed to environmental smoking may also be subject to changes in drug metabolism because of the induction of hepatic CYP1A2 enzymes [34]. Alternatively, dosage reduction may be required if CYP1A2 inhibitor drugs, such as amlodipine, cimetidine, ciprofloxacin, diclofenac, fluoxetine, fluvoxamine, or nifedipine are added to the therapeutic regimen or if patients stop smoking [31,34]. When smoking cessation occurs, the downregulation of the CYP1A2 enzymes occurs, depending mainly on the degree of change in cigarette smoking status compared to baseline [32]. Therefore, it is essential to consider how quickly CYP1A2 enzymes return to normal after stopping smoking [31,34]. The turnover time of the CYP1A2 enzymes is about two days, and it usually takes

several weeks to return the induction of CYP1A2 enzymes to normal metabolism [32,34]. Therefore, within two to three days after smoking cessation, it may be essential to have an empirical dose reduction [32]. However, smoking cessation reduces propranolol clearance by about 77.0%, but the clinical effects of high plasma concentrations of the drug are difficult to anticipate [33] because propranolol dosage varies from 80 to 640 mg per day [33]. Therefore, it is essential to monitor the signs and symptoms of propranolol overdose, such as bradycardia, fatigue, dizziness, and others, to consider a dose reduction of propranolol [33]. Nicotine has no role in the induction of hepatic CYP1A2 enzymes [34]. Therefore, using nicotine replacement therapy (NRT) products to help smoking cessation does not contribute to pharmacokinetic drug interaction as smoking [33,34]. However, nicotine appears to have a role in pharmacodynamic interaction with beta-adrenergic antagonists [31].

### Influence of cigarette smoking on the pharmacodynamic characteristics of drugs

Besides pharmacokinetic interaction between smoking and beta-adrenergic antagonists, pharmacodynamic interactions may also occur [8]. Pharmacodynamics means "what the drug does to the body", where pharmacodynamic interactions usually occur between drugs with either additive or opposing effects [30]. Mostly, the brain is the organ that suffers from pharmacodynamic interactions [30]. Smoking can contribute to such an interaction through the pharmacological effects of nicotine that may interfere with the therapeutic response to drugs [8,38]. As mentioned earlier, nicotine acutely raises blood pressure, heart rate, and myocardial contractility [25,38]. As a result of these effects, smoking reduces beta-adrenergic antagonists' effectiveness in controlling heart rate and blood pressure in smoker patients [8,38]. Thus, these drugs may require a higher dose rate to achieve therapeutic responses [8]. Another beta-antagonist, nebivolol, has beta-blocking and vasodilation effects [27]. The drugs also increase the forearm blood flow indicating a potential beneficial impact on smoking-induced endothelial dysfunction because of nicotine [38]. However, it was limited only to light smokers [5].

The acute effects of nicotine on the cardiovascular system, particularly an increase in heart rate, are identical between low and high nicotine levels [8]. Therefore, such interaction can still exist in continuing or reducing the number of cigarettes smoked [8]. However, the maximum plasma concentration of nicotine is established quickly, within 5 minutes after cigarette smoking, which is responsible for nicotine's immediate maximal pharmacodynamic effect through tobacco smoking [32]. Based on the evidence, upon smoking cessation, such kind of drug interaction is less likely to occur [8]. As the half-life of nicotine is about 2 hours, there is a rapid decrease in the acute pharmacological effects of nicotine [8]. Anderson and Chan [32] reported that the bioavailability of nicotine from cigarette smoking is about 80.0-90.0% higher than from products of NRT, which is about 55.0% from nicotine inhalers, 70.0% from nicotine nasal spray, 51.0%-78.0% from nicotine gum and 68.0%-100% from nicotine transdermal patches [32]. However, the products of NRT can raise heart rate by up to 10 to 15 beats and blood pressure by about 5 to 10 mmHg with less acute effect possibly obtained from transdermal nicotine patch [8]. Nicotine concentrations from NRT are between one-third to two-thirds of cigarette smoking [8]. These lower nicotine concentrations may render the pharmacodynamic drug interactions of NRT less clinically significant [8].

### Smoker elderly patients and drug interactions

Old age is an additional factor that influences the extent of drug interaction, particularly between beta-adrenergic antagonists and smoking [5,39]. Careful attention to elderly patients is needed, as with old age, there is a high prevalence of comorbid conditions with increasing numbers of prescribed drugs [33,39]. There are also changes in the pharmacodynamic effects of drugs, such as raising the activity of certain medications, such as central nervous system depressants at specific plasma concentrations [33]. The alteration of pharmacokinetics parameters in the elderly is of particular concern with the absorption of drugs, reducing renal drug elimination and hepatic drug clearance with alterations in body water and fat content [33]. These changes raise the drug's half-life, which ultimately increases the risk of the drug's toxicity and adverse effects, thus making the safety and efficacy of medications after smoking cessation challenging to predict [33,39]. In elderly patients, metabolic changes in response to propranolol infusion exist, reducing its effectiveness [5]. Physiologically, it might be related to the impairment of the autonomic nervous system by disturbing the sensitivity of the baroreceptor reflex and reducing its function as a consequence of rising aortic stiffness [5]. Which adversely impacts elderly patients when they are exposed to smoking [5].

## Conclusions

Cigarette smoking exerts potential impacts on blood pressure through several mechanisms. The presence of confounding factors further masks the clear relationship between cigarette smoking and the elevation of blood pressure. Cigarette smoking can interact with antihypertensive drugs, primarily with beta-adrenergic antagonists. The interaction occurs through pharmacokinetic and pharmacodynamic mechanisms. Therefore, as smoking continues to persist globally, it is essential to monitor patients' smoking status in hospitals or outpatient clinics and to consider the dosage modification of beta-adrenergic antagonists according to their smoking status. This would ensure the effective and safe use of beta-antagonists for the treatment of hypertension in both active and passive smokers, with particular attention to elderly patients. Further studies are required to emphasize the effect of cigarette smoking on different beta-antagonists used for the treatment of hypertension in both active and passive smoker patients.

### Abbreviation

WHO: World Health Organization; LMICs: Low- and middle-income countries; ISH: International Society of Hypertension; CYP: Cytochrome; PAHs: Polycyclic aromatic hydrocarbons; UDP: Uridine 5’-diphosphate; UGT: Uridine diphosphate (UDP)-glucuronosyltransferases; NRT: Nicotine replacement therapy.

### Declaration

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## Availability of data and materials
Data will be available by emailing halafouad9020@uomosul.edu.iq.

## Authors' contributions
Hala F. Kasim (HFK) is the principal investigator of this manuscript (Review Article). HFK is the author responsible for the study concept, design, writing, reviewing, editing, and approving of the manuscript in its final form. HFK has read and approved the final manuscript.

## Ethics approval and consent to participate
We conducted the research following the Declaration of Helsinki. However, Review Articles need no ethics committee approval.

## Consent for publication
Not applicable

## Competing interest
The authors declare that they have no competing interests.



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