Introduction

Tobacco use is very common in most countries and is considered one of the leading causes of premature death worldwide (1). Smoking is a serious worldwide public health problem that can cause various non-communicable diseases such as cancer, cardiovascular diseases, asthma, and emphysema (1,2).

Smoking has adverse effects on the health of smokers and secondhand smokers, and it challenges health centers when designing therapeutic interventions (3). Sometimes tobacco use interacts with medications and the dose should be adjusted more precisely due to drug interactions.

Drug interactions are among the most important treatment challenges in which the drug effectiveness is likely to be altered by drugs, foods, beverages, or other substances used concomitantly (4).

According to the American Medical Association, 7000 deaths occur annually due to drug side effects, most of which are due to drug interactions. The risk of occurrence and severity of drug interactions are influenced by factors such as the number of medications, treatment duration, patient age, number of physicians, and the disease stage (5).

Drug interactions can be pharmacokinetic or pharmacodynamic. In pharmacokinetic interactions, the plasma concentration of a drug changes, but in the pharmacodynamic interactions, the specific function of a drug changes without a change in its plasma
concentration. Drug interactions can reduce the drug effectiveness, or even increase the plasma concentration and potential toxicity of a drug, leading to minor or serious unexpected side effects (6).

Tobacco use can affect the effectiveness of drugs by pharmacokinetic and pharmacodynamic mechanisms. Tobacco use can also cause pharmacokinetic interference that alters the absorption, distribution, metabolism, or elimination of drugs, potentially altering the drug response. Consequently, smokers may need higher doses of medications. Quitting tobacco use may require dose reduction (7). In addition, it is hypothesized that pharmacodynamic interactions with tobacco smoking can alter drug effectiveness (5,8).

In the present study, the molecular mechanisms of tobacco-related drug interactions were investigated. In addition, common relevant drug interactions were investigated.

The aim of this study was to investigate the effect of smoking on drug metabolism and plasma drug levels and whether smokers need to fine-tune the dose.

Materials and Methods
In this review, ScienceDirect, PubMed, SciELO databases, and Google Scholar search engine were searched without time limit using MeSH keywords (smoking, tobacco, reabsorb, distribution, metabolism, elimination, and drug-tobacco interaction). The search included research articles as well as review articles. In the initial search, 54 articles were selected and finally 22 articles were used. Articles that were not related to the objectives of the study, published in non-English languages, and did not have free full-text access were excluded from the study. Then, the articles were studied and the key points of each article were identified.

The Potential Mechanisms of Interaction
Tobacco smoke contains about 7000 chemical compounds, including hazardous chemicals such as polycyclic aromatic hydrocarbons, ammonia, aromatic amines, phenols, carbonyls, hydrocyanic acid, and nitrosamines (9). Many compounds, such as nicotine, polycyclic aromatic hydrocarbons, carbon monoxide, and heavy metals, are potent enzyme inducers and may affect the drug bioavailability by accelerating metabolic clearance (10). Increasing the clearance of several liver-metabolized drugs is an important factor in dose-adjustment strategies (11). Polycyclic aromatic hydrocarbons, which are the products of incomplete combustion of organic matter through smoking (12), are probably responsible for inducing enzymes in cytochrome p450 enzyme systems such as CYP1A1 and CYP1A2 (11,13-18). In addition to the CYP1A family, CYP2E1 induction is mediated by smoking based on limited data (12,14). However, it is not clear whether polycyclic aromatic hydrocarbons or other components in tobacco smoke, such as toluene, induce its activity (12). CYP450 enzymes are hemoproteins responsible for drug metabolism, detoxification of xenobiotics, and activation of carcinogens (15,17). P450 enzymes are responsible for drug metabolism in the first stage by oxidation of the main compound to an excreted metabolite (14,15). Therefore, drug interactions with tobacco smoking is mostly due to the induction of drug metabolism (16,18).

Uridine 5’-diphospho (UDP)-glucuronosyltransferases (UGTs) are a family of enzymes that catalyze glucuronidation reactions (second phase conjugation) (19). Polycyclic aromatic hydrocarbons of tobacco smoke may also induce UGT (20).

CYP1A2 accounts for about 15% of the total hepatic CYP content (11,17). Low CYP1A2 expression also occurs in the esophagus, stomach, and large intestine, but not in the small intestine (11). It also metabolizes about 15% of drugs such as clozapine, theophylline, tacrine, and zolmitriptan. Genetic polymorphisms in the CYP1A2 gene cause extensive interpersonal variation in drug metabolism and may contribute to the development and spread of cancer (17). The induction of CYP1A2 in heavy or moderate smokers may be higher than in light smokers (for example, less than 10 cigarettes per day) (13,17). On the other hand, CYP1A1 is an extrahepatic enzyme in humans, which is downregulated in the lungs, gastrointestinal tract, kidneys, and placenta, but is undetectable in the liver (12,17).

The most common CYP isoforms related to the metabolism of systemic therapy in lung cancer include CYP1A1, CYP1A2, CYP2D6, CYP3A4, and some UDP isoforms of glucuronyl transferase (17). CYP1A1 and CYP1A2 are involved in the metabolism of almost all anticancer drugs (10). Both CYP1A1 and CYP1A2 are regulated by the aromatic hydrocarbon receptor (AhR). The binding of polycyclic aromatic hydrocarbons to AhR results in the transfer of the -AhR complex to the nucleus by means of the Ah (Arnt) nuclear transmitter receptor. This heterodimer then interacts with the reactive xenobiotic element in the promoter region of CYP1A1 and CYP1A2 genes, which in turn activates gene transcription, increases the translation of CYP-specific enzymes, and accelerates drug metabolism and clearance, affecting clinical outcomes (12,15). Since AhR mRNA is often expressed in the placenta, lung, heart, pancreas, and liver, the induction of CYP1A enzymes can occur by exposure to polycyclic aromatic hydrocarbons during smoking (12). Even second-hand smokers may experience changes in drug metabolism (13).

Polycyclic aromatic hydrocarbons can change transcription factors such as NHHF4α and HNF1α epigenetically, leading to the up-regulation of CYP1A2. Cigarette smoke induces chromatin remodeling to facilitate gene expression by acetylating lysine residues.
on histone proteins. In addition, decreased activity of histone deacetylases, which remove acetyl groups for transcriptional suppression, has been seen in bronchial biopsies of smokers compared with non-smokers (15).

Human liver CYP2D6 accounts for 4% of total cytochrome P450 enzymes. Despite its small percentage, CYP2D6 plays a major role in drug metabolism. For example, the main drugs involved in metabolism include tricylic antidepressants, serotonin reuptake inhibitors, neuroleptic drugs, beta-blockers, and antiemetic drugs (17).

CYP3A4 is apparently the most important P450 enzyme for drug metabolism in humans. It is responsible for the metabolism of more than 50% of the drugs used in systemic therapies for lung cancer, including taxanes, gefitinib, and erlotinib. Increased transcription of this enzyme gene leads to an increase in the activity of enzymes, which in turn can affect the pharmacokinetics of drugs that are metabolized by the CYP3A4 isofrom (15,17).

When smokers quit smoking or are forced to quit smoking, symptoms of changes in drug metabolism can occur within a few days and the serum concentration of the drug increases (13). Because the CYP1A2 circulation time is slightly shorter than 2 days, a significant clinical effect can be detected within a week of quitting smoking. Experimental reduction of the drug dose may be necessary within 2–3 days after smoking cessation (12). Authors recommended a 10% daily-dose reduction for CYP1A2 substrates until the fourth day after quitting smoking. The effect of drug metabolism may last for weeks to a month after smoking cessation. Therefore, there may be a delay until CYP1A2 enzymes return to normal hepatic metabolism. The dose of potentially toxic drugs should be reduced immediately when a heavy smoker quits smoking (13).

While pharmacokinetic drug interactions associated with tobacco smoking occur through the induction of CYP and UGT enzymes, pharmacodynamic interactions are mediated by nicotine (14). Nicotine can directly affect the molecular effectors of cellular apoptosis induced by several chemotherapy treatments for lung cancer. Nicotine is not carcinogenic, but its metabolites can contribute to tumor growth. Nicotine can upregulate the expression of some growth factors such as TGFβ and VEGF, which are involved in neoangiogenesis, and downregulate TGF-beta, which helps tumor cells to proliferate (15,17).

Chemical resistance is a major concern in the therapeutic response to cancer. Some components of cigarette smoke along with nicotine are responsible for treatment failure. Nicotine is thought to play an important role in preventing the effects of chemotherapy by improper (down) regulating proapoptotic proteins such as Bax and Bad and up-regulating anti-apoptotic proteins (10).

**Antipsychotic Drugs**

Clozapine and olanzapine are second-generation antipsychotic drugs used for refractory schizophrenia (11,14). These two drugs are metabolized by CYP1A2. Clozapine has also been reported to be metabolized by UDP-glucuronosyltransferase 1A1 (UGT1A1) and UGT1A4 (14), in addition to CYP2C19 and CYP3A4 (11), while olanzapine is metabolized by UGT1A4 (14). Approximately, 70% to 80% of schizophrenia patients smoke and the plasma concentrations of clozapine and olanzapine are reduced in smokers because the polycyclic aromatic hydrocarbons of tobacco smoke strongly metabolize them through CYP1A2 and UGT enzymes (13,18).

A daily consumption of 7–12 cigarettes is probably sufficient for maximum induction of clozapine and olanzapine metabolism, and smokers have 40%-50% lower serum concentrations than non-smokers. On the other hand, when a patient quits smoking, the clozapine and olanzapine doses may need to be reduced by 30%-40% to prevent an increase in serum concentrations and the risk of toxicity (13).

**Antidepressant Drugs**

All antidepressant drugs are metabolized by different types of cytochromes in the liver. With regard to the class of selective serotonin reuptake inhibitors, citalopram is metabolized by CYP 2C19 and A43, fluoxetine by D6 2, 3A4, and C92, fluvoxamine by A21 and D62, escitalopram by C19 2, 2D6, and A43, and sertraline by D6 2, 3A4, 2C9, and C192. In the case of selective serotonin and norepinephrine reuptake inhibitors, venlafaxine is metabolized by CYP 2D6, 3A4, and C92, duloxetine by D62 and A21, and trazodone by CYP 2D6. Mirtazapine, as a tetracyclic antidepressant, is metabolized by A21, 2D6, and A43, and bupropion by B62. Besides, UGT enzymes were found to be somehow involved in mirtazapine metabolism. Imipramine, a tricyclic antidepressant, is first metabolized by CYP2C19 and then by CYP1A2 (14,16).

Polycyclic aromatic hydrocarbons in tobacco smoke reduce serum concentrations of fluvoxamine, duloxetine, and imipramine by inducing CYP1A2-induced metabolism. Therefore, doses of these drugs should be increased in smokers (14,16). Serum levels of mirtazapine and its main active metabolites (S-mirtazapine and RN-desethyl mirtazapine) can be reduced in smokers due to the induction of its metabolism by CYP1A2 UGT (14,16). It has been shown that CYP1A2 is involved in 8-hydroxylation and possibly N-oxidation of mirtazapine (16). Results of previous experiments on sertraline, escitalopram, citalopram, and bupropion showed no effect of smoking on their pharmacokinetics (16).

However, one study showed lower serum escitalopram concentrations in smokers than in non-smokers, even if smokers have received higher doses of the drug. This decrease in concentration may be due to the induction
of CYP2C19 and CYP3A4 by tobacco smoke. In this study, CYP2C19 and CYP3A4, as the two main enzymes in esocitalopram metabolism, and CYP2D6 accounted for 23%, 35%, and 28% of the net clearance, respectively. In addition, because esocitalopram is a p-glycoprotein substrate, it is vulnerable to drug-drug interactions (18).

Another study revealed no difference between the two groups in terms of fluoxetine concentration, but the concentration of its active metabolite, norfluoxetine, was higher in smokers. Because norfluoxetine is an active metabolite, such a relationship could affect patients' responses to fluoxetine use and its consequences by increasing the half-life of the molecule. For example, it can cause drug bioaccumulation and serotonin syndrome (16).

The data show that smoking causes a decrease in the serum concentration of trazodone, but it has no effect on the serum concentration of its active metabolite, i.e., m-chloro-phenylpiperazine. This decrease may be due to the increased hydroxylation and N-oxidation of trazodone caused by polycyclic aromatic hydrocarbons from cigarette smoke (16).

Overall, the available evidence shows a decrease in serum concentrations of fluvoxamine, duloxetine, trazodone, mirtazapine, and imipramine in smokers compared to non-smokers. Quitting smoking in smokers who are taking such drugs may lead to an increase in their serum levels. Such an increase may cause side effects that have not been present before. Most side effects of antidepressants are dose-dependent, and some occur only when the serum antidepressant level reaches a certain level (16).

Erlotinib
Erlotinib is a tyrosine kinase inhibitor receptor, which acts on the epidermal growth factor receptor. It is approved for non-small cell lung cancer (NSCLC) treatment (10,14,15,17) and blocks the progression of the cell cycle in the G1 stage (15). Erlotinib is mainly metabolized by CYP3A4 and to a lesser extent by CYP1A2 and CYP1A1 (14,15,17) through demethylation of side chains and oxidation to carboxylic acid metabolites (15).

Plasma erlotinib concentrations in smokers are significantly reduced by cigarette smoke, which may be due to increased metabolism of erlotinib by CYP1A2 and CYP1A1 (10,14). This figure was reported to be 2.8 times lower in smokers, and oral clearance was 24% faster than non-smokers. The overall survival time in non-smokers who used this drug was more than 12 months longer than in current and former smokers (10).

Irinotecan
Irinotecan is a topoisomerase-I inhibitor used to treat NSCLC as well as a substrate for several cytochrome P450 and UGT1A1 isoenzymes. Smokers experience significantly less irinotecan-related toxicity and side effects. The incidence of grade 3/4 neutropenia was reported to be 6% in smokers and 38% in non-smokers. Smoking reduces both the body's access to irinotecan and treatment-induced neutropenia, indicating a potential risk of treatment failure (15,17).

Irinotecan clearance in smokers is 18% higher than in non-smokers. Besides, its glucuronidation-based metabolism is higher in smokers than in non-smokers (10). Decreased systemic exposure to the active metabolite of irinotecan is observed in smokers. However, it is not clear whether it affects the response of lung cancer to irinotecan (15).

Gemcitabine
Gemcitabine is a prodrug, a deoxycytidine analog that requires intracellular uptake and phosphorylation to be activated (15,17). It is phosphorylated to gemcitabine monophosphate (dFdCMP) by deoxycytidine kinase, which is then converted to active metabolites, i.e., gemcitabine di- and triphosphate nucleosides (dFdCDP and dFdCTP). This nucleoside analog shows cytotoxic effects by inhibiting DNA synthesis (15).

Gemcitabine is converted to the inactive metabolite, i.e., difluorodeoxyuridine (dFdU) by cytidine deaminase. Smoking-induced cytidine deaminase overexpression may increase catabolism and decrease the effect of gemcitabine in smokers and former smokers. The incidence of grade 3/4 neutropenia was much higher in patients without a history of smoking than in those with a history of smoking. Therefore, patients without a history of smoking may be at higher risk for gemcitabine-induced neutropenia (15,17).

Caffeine
Caffeine is mainly metabolized by the enzyme CYP1A2. CYP1A2-mediated caffeine metabolism is increased in smokers, and smokers may usually consume more coffee or other caffeinated beverages due to increased caffeine clearance (13,14).

When patients quit smoking, increased serum caffeine levels may cause anxiety, irritability, restlessness, insomnia, tremors, palpitations, and tachycardia. Caffeine poisoning can also mimic the symptoms of nicotine withdrawal. Therefore, smokers are advised to reduce their caffeine intake by half to avoid side effects when quitting smoking (13). In a study that was conducted on eight male and four female heavy smokers (smoking at least 20 cigarettes a day), CYP1A2 activity was measured by caffeine clearance, and results showed 12.3, 20.1, 25, and 28.2% reduction from baseline on days 1, 2, 3, and 4 after abrupt smoking cessation (12).

Clopidogrel
Clopidogrel binds irreversibly to P2Y12 adenosine diphosphate receptors and inhibits platelet function. It
is a prodrug that is first converted to 2-exoclopidogrel by CYP1A2, 2B6, and C19, and finally to the active metabolite by CYP2B6, 2C9, 2C19, and A4. Therefore, CYP2C19 and A43 are the most important enzymes for clopidogrel metabolism. However, a number of clinical trials showed that the clinical response and the final progress in clopidogrel treatment in smokers are improved. One study reported that platelet inhibition was significantly higher in smokers (12).

Propranolol
Propranolol is a beta-adrenergic receptor antagonist. Propranolol is known as a substrate for CYP1A2 and CYP2D6 (21). Propranolol glucuronidation increases in smokers (15). Plasma propranolol concentration decreased in smokers (22) but it increased in patients who had quit smoking (23).

Warfarin
Warfarin is an anticoagulant that is widely used to prevent thromboembolic events. Warfarin is primarily metabolized by CYP1A2 (24). Tobacco smoke may increase R-warfarin metabolism and decrease its effectiveness. Smoking cessation may require careful monitoring of patients treated with warfarin (25).

Ropinirole
Ropinirole is a dopamine agonist which has been approved for the treatment of Parkinson’s disease. Ropinirole is mainly metabolized by CYP1A2, and plasma ropinirole concentrations in smokers may be reduced due to increased CYP1A2-mediated metabolism (26). In a case report of a woman treated with ropinirole, the results showed significant side effects, including excessive night sweats 4 days after smoking cessation (12). Adjusting the dose of ropinirole after smoking cessation may be necessary (27).

Hormone Replacement Therapy
Tobacco smoke can increase the hepatic clearance of oral estrogens and reduce the therapeutic effect of hormone replacement therapy (HRT) on hot flashes, osteoporosis, genital symptoms, and cholesterol. Female smokers are advised to use transdermal HRT, which bypasses hepatic metabolism (28).

Overall, smokers may need higher doses of drugs such as clozapine, olanzapine, haloperidol, chlorpromazine, fluvoxamine, duloxetine, mirtazapine, imipramine, theophylline, aminophylline, caffeine, rociguit, erlotinib, tacrine, warfarin, propranolol, ropinirole, mexitetine, frovatriptan, zolmitriptan, alogeron, flutamide, melatonin, ramelteon, tasimelteon, rasagiline, tizanidine, triamterene, ropivacaine, methadone, and oral estrogens due to increased CYP1A-mediated metabolism and should be monitored for drug toxicity and dose when quitting smoking (14).

Conclusion
In previous studies, the metabolic rate of various drugs such as antipsychotics and antidepressants as well as drugs such as erlotinib, irinotecan, gemcitabine, caffeine, clopidogrel, propranolol, warfarin, ropinirole, estrogens, and so on has been studied in smokers and non-smokers. The results of studies showed that serum antipsychotic levels in smokers are about 40%-50% lower. However, the information on antidepressants was very different and the serum level of some drugs was lower. Additionally, the serum levels of the active forms of prodrugs, which were activated after metabolism, were higher and the dose needed to be reduced. The effects of smoking on citalopram, escitalopram, sertraline, and bupropion were not very obvious and could not be cited.

The metabolism of erlotinib and irinotecan was faster in smokers. Significantly less toxicity and drug side effects were seen in smokers than in non-smokers. Studies on the metabolism of caffeine, clopidogrel, propranolol, warfarin, ropinirole, and HRT showed almost the same results, and smokers had lower serum levels of the drug.

It can be concluded that smoking affects the speed of drug metabolism. In most cases, smokers had lower serum levels of the drug; therefore, these people needed higher doses. This is especially important for people who want to quit smoking because the dose must be reduced over time, otherwise, the risk of poisoning and side effects will be high.

Acknowledgments
The authors acknowledge Hormozgan University of Medical Sciences.

Authors’ Contribution
ER, KJR, DP and ASA participated in data collection, investigation and literature review and original draft writing; MF and HA project administration, review writing, and editing.

Conflict of Interest Disclosures
The authors declare no competing interests.

Ethical Statement
Not applicable.

Funding
None.

Informed Consent
Not applicable.

References