EFFECT OF THE IMPURITIES ON DRUGS, METABOLISM, AND THE ROLE OF THE ISOENZYME CYP3A4

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Abstract. *Medicinal drugs have found great use in health treatment, and their use has increased after the COVID-19 pandemic. The health crisis caused by the coronavirus made the national authority for the control of medicinal drugs in Kosovo activates the institutional mechanisms for the control of drugs. Analyzing the excessive concentration of heavy metals in drugs and the adverse effects on the body since they reduce the positive effects of the drug.* **Methods.** *The research was conducted during the years 2020-2022 in Kosovo, the samples (over 30 patients) were studied, in 40 medical examinations, how the cytochrome P450 enzymatic system works and the impact on anti-inflammatory drugs. These drugs are metabolized by cytochrome CYP4502C9, which carries multiple inherited polymorphisms in the coding sequences, and by two varieties of this enzyme (cytochrome), CYP4502C9*2/3.* **Results.** *The presence of heavy metals in drugs is a concern related to neurotoxicity, nephrotoxicity, hepatic toxicity, cardiovascular effects, immunotoxicity and carcinogenicity. The control of the content of elemental impurities is an important aspect of the quality assurance system of medicines and human health. Analytical studies of the amount of heavy metals in paracetamol samples X1 and X2 for the five metals studied, Arsenic in sample X1 showed a high presence of elements with a value of 5.07% among other metals. Nickel varies with a value of 4.91% in paracetamol X2 samples, the highest value for the analyzed plants. The analytical results of the studied medicinal plant "Matricaria Chamomilla" showed that the presence of Lead has a value of 3.7% compared to other metals in medicinal plants, while Mercury varies with 4.7%).* **Conclusions.** *Impurities in drugs often have unwanted or toxic effects on human health. Nowadays, knowledge about the negative effects of heavy metals is important for human health. Heavy metals enter the grass chain during the production process and impurities from natural raw materials.*

Key words: drugs, metabolism, safety and human health

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INTRODUCTION

The process of quality production of drugs is complicated. Drug discovery and development is a costly and time-consuming process [1, 2]. According to the Center for the Study of Medicine, developing a new drug takes more than 10 years of scientific research and spending about 2.6 billion dollars. Living beings are constantly in contact with various toxins, but in most cases, we are able to resist them thanks to the perfect mechanisms that our organism possesses [3]. One of these mechanisms

is a very important group of enzymes discussed in this paper. With the emergence of the COVID-19 pandemic, Kosovo has fallen from the 10th place to the 19th place, the control of the quality of drugs and the use of antibiotics without control [4]. The appearance of the pandemic has increased the demand for the use of antibiotics. Antibiotic resistance is a public health challenge for citizens with socioeconomic implications, considering the unnecessary use of antibiotics and over-the-counter sales [5]. While producing pharmaceutical products, researchers must be able to reduce impurities in pharmaceutical products [5]. Chemical reagents during analytical processes create or increase the concentration of impurities in drugs, causing the drugs produced not to have high purity [6].

Pharmaceutical companies, as a result of old technologies, the impurity of raw materials during the drug production process create a problem in the quality of drugs, "e.g." the amount of metal (palladium) in the herb Ramipril (ACE inhibitor), maximum value. The amount of metal (palladium) in the drug Ramipril (ACE inhibitor), the maximum value should be 20 ppm; in the drug Acitretin ($C_{21}H_{26}O_3$), the maximum value is 10 ppm. Should be 20 ppm in the drug Acitretin ($C_{21}H_{26}O_3$), the maximum value is 10 ppm [7]. The purpose of the study is to analyze heavy metals in pharmaceutical products, find the main sources of chemical impurities during the drug production process and compare with natural drugs [8].

MATERIALS AND METHODS

Subjects

In ancient times, metals were used as medicine to cure some diseases [9]. The results of studies show that the presence of heavy metals such as lead and cadmium in medicines causes serious risks to human health in low doses. More prolonged exposure to metals negatively affects human psychological activities [10]. Cytochrome 3A4 is a member of the cytochrome P450 enzyme family, while the CYP3A4 enzyme is more important than the P450 enzyme. Since it metabolizes a wide range of xenobiotics with different structures, including more than 50% of all clinically important drugs (Fig. 1). The role of the CYP3A4 enzyme in the body metabolizes more than 1900 drugs (1033 enzymes act as substrates, 696 act as inhibitors and 241 as inducers of the CYP3A4 enzyme [11].
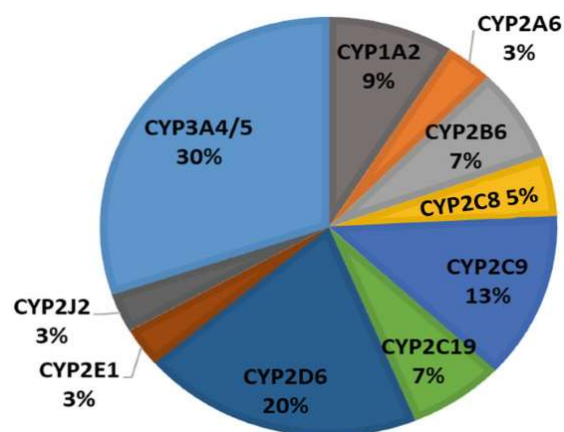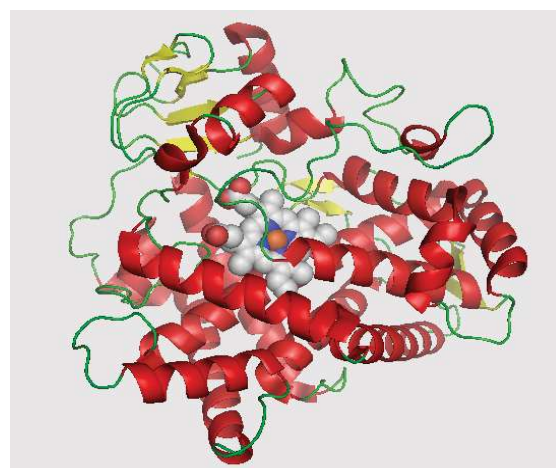
Note: Characteristics of Major Drug Metabolizing Cytochrome P450 Enzymes Kevin M. Johnson, Dian Su & Donglu Zhang [11]

Fig. 1. Cytochrome (CYP) P450 enzymatic system

We are exposed to many xenobiotics originating from pesticides, insecticides, herbicides, heavy metals, radioisotopes, aerosols, and various oxides. CYP enzymes are central membrane-bound proteins responsible for phase I reactions or biotransformation [12]. This enzyme is mainly found in the liver (~40% of total hepatic CYP content), small intestine, colon, prostate and other parts of the human body. The CY3A4 enzyme is the most active CYP (Cytochrome) enzyme in the gut. Due to intestinal metabolism, some drugs that are substrates of the CYP3A4 enzyme have low oral (but not intravenous) bioavailability. The bioavailability of these substrates is dramatically altered by inhibition, induction, or saturation of the CYP3A4 enzyme (Table 1). CYP3A4 enzyme activity is absent in neonates but reaches adult levels over one year of age [13]. Clinical studies show that women metabolize drugs that are substrates of the CYP3A4 enzyme faster than men (20-30% increase). Analyzes have shown approximately two-fold higher levels of CYP3A4 protein or enzyme in female compared to male tissue samples (Figure 1).

Table 1. Tabular presentation of drugs metabolized by CYP 3A4 enzyme

Corticosteroids	Immunosuppressants	Opioid	Antihypertensive drugs	Cancer drugs	Cholesterol-lowering drugs
Flutikazon	Ciklosporina	Sufentanil	Felodipina	Endoxifen	Simvastatin
Propionat	Tacrolimus	Metadon	Nifedipina	Tamoxifen	Atorvastatin
	Sirolimus			Sunitinib	Lovastatin

Relatively recently (1998), scientists discovered that elements in grapefruit had strong inhibitory activities of the CYP3A4 enzyme, interacting with more than 44 drugs. The effects last from 3-7 days, with the greatest impact on the patient within 24 hours of consuming the drug. Enzymes oxidize several substances using iron as a catalyst and are able to metabolize a wide variety of substances. Cytochrome P450 enzymes are hemoproteins bound to the membrane and play a key role in metabolic processes (Fig. 2).

This study was conducted during the years 2020-2022 in Kosovo, samples (over 30 patients) were studied, in 40 medical examinations, how the cytochrome P450 enzymatic system works and the impact on anti-inflammatory drugs [14]. These drugs are metabolized by the CYP4502C9 enzyme, which carries multiple inherited polymorphisms in the coding sequences, and by two varieties of this enzyme, such as CYP4502C9*2/3. People who have the *2 allele are at increased risk of bleeding because the *2 allele reduces the activity of the enzyme to a greater degree. There are inter-ethnic differences in the frequency of CYP5402C9 alleles. The impact of some xenobiotics on the cytochrome P450 enzymatic system [15]. The presence of some xenobiotics plays a role in accelerating the cytochrome P450 enzymatic system, such as: arabamazepine, rifampin, alcohol, phenytoin, griseofulvin, phenobarbital, sulfonylurea, which affect the P450 enzyme. [16]. If a substance is taken, such as xenobiotics such as phenytoin (chemicals), the metabolism process develops so quickly that the drug will not have a slowing or inhibitory effect as Valproate, Ketoconazole, Isoniazid, Sulfonamide, Chloramphenicol, Amiodarone, Erythromycin, Quinidine, Grapefruit [17]. The working methods for analyzing heavy metals in drugs are analytical methods and Inductively Coupled Plasma – Mass Spectrometry (ICP-MS) methods. Reagents used standard elemental solvent (1 g/l) for metals Cd, Pb, Ni, and concentrated nitric acid (HNO3 1%) is also used. Analytical methods such as ICP-MS for metal analysis play an important role in identifying elemental impurities in drugs. The method also identifies the specific quantity for each element that results are expected in this study (Table 2).
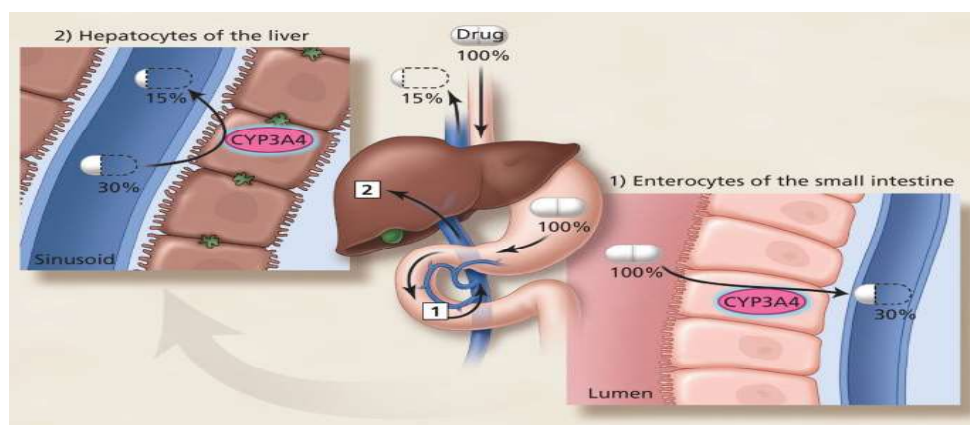
Note: Image courtesy of Christine Kenny (Grapefruit–medication interactions: Forbidden fruit or avoidable consequences? David G. Bailey, George Dresser, and J. Malcolm O. Arnold. doi: 10.1503/cmaj.120951.

Fig. 2. The influence of grapefruit juice on CYP 3A4 enzyme activity and the role of the P450 enzyme system

Table 2. Tabular presentation of some drugs containing traces of heavy metals

The name of the drug	Heavy trace elements
Vitamin	Ni, Cr, Pb
Ethambutol	Fe, Cr, Ni, Cu,Co, Mn
Multivitamin	Cu, Mg, Mn, Se, Zn,Cr
Methamphetamine hydrochloride	Br, Pd, Ba, Sb, Na
Enalapril maleate	Co, Pd. Pt, Rh
Dietary supplement	Ni, Pb, Cd, Hg, As

The possibility of drug toxicity is numerous; the contamination factors are:

– Probability of using chemical reagents in drug production processes;

– The presence of impurities isolated with other elements in the raw materials for the production of drugs or chemical reagents;

– Elemental impurities in natural materials used for pharmaceutical products;

– Environmental distribution of elements depending on geological areas [18].

RESULTS

The concentration of heavy metals in drugs is a concern for human health related to neurotoxicity, nephrotoxicity, hepatic toxicity, cardiovascular effects, immunotoxicity and carcinogenicity [19].Controlling the content of elemental impurities in drugs is important for pharmaceutical companies, usually for the quality assurance system of drugs and human health. The use of drugs as medicine or foods with a high presence of lead and other toxic elements increases the concentration of these metals in the human body and the consumption of nutritional products such as turmeric root [20]. The high concentration of toxic metals in drugs increases during the growth phase of the plant geological soil with the presence of lead and other toxic elements [21]. The use of green tea with a high presence of lead in green tea leaves increases the presence of lead in the body in (Table 3).

In this study, the presence of heavy metals Green tea for Pb ranges from the lowest value of 4.616-20.75 mg.kg-1. Ni varies with the value of 4.442-20.29 mg.kg-1. Cd, varies with the value 4.571-20.11. As, varies with the value of 3.124-19.89, Hg, varies with the value of 4.231-20.21 mg.kg-1. Analytical results show values above international norms in (Table 3). Paracetamol is a drug that has been found to be very useful in treating rheumatic fever or pain from various inflammations. Excessive amounts of heavy metals in paracetamol have negative effects on the body due to the fact that they reduce the positive effects of the drug. Testing metals in drugs according to the USP < 231 > method (Method Validation for Quantitative Heavy Metals Testing) is a simple test for the identification of heavy metals in drugs and the identification of impurities in drugs. The identification of heavy metals can be done up to the concentration value (1ppb) in (Fig. 3).

Analytical studies of the amount of heavy metals in paracetamol samples X1 and X2 for the five metals studied, Arsenic in sample X1 showed a high presence of elements with a value of 5.07% among other metals. Nickel varies with a value of 4.91% in paracetamol X2 samples, the highest value for the analyzed plants. The analytical results of the studied medicinal plant "Matricaria Chamomilla" showed that the presence of Lead has a value of 3.7% compared to other metals in medicinal plants, while Mercury varies with 4.7%. The high concentration of heavy metals in some studied samples is an indication that these drugs are often terrestrial and harmful to hu-

Table 3. Determination of heavy metals with spectrometric methods than atomic absorption

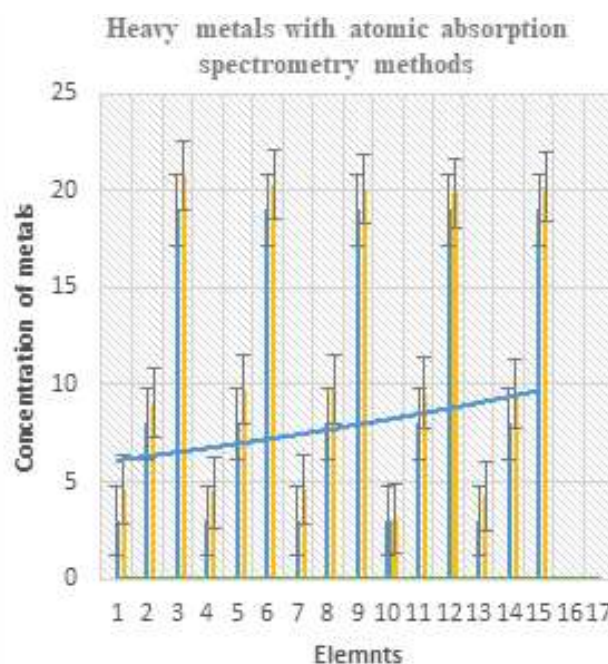| Metals	The amount added to the powder (mg.kg⁻¹)	Results (mg.kg⁻¹)
Leaden	3	4.612
	8	9.114
	19	20.75
Nickel	3	4.442
	8	9.782
	19	20.29
Cadmium	3	4.571
	8	9.783
	19	20.11
Arsenic	3	3.124
	8	9.594
	19	19.89
Mercury	3	4.231
	8	9.513
	19	20.21

Fig. 3. Graphic representation of heavy metals with spectrometric methods than atomic absorption

Table 4. Tabular results of heavy metals in paracetamol samples (X1, X2)

Metals	X1 Concentration of heavy metals (µg/ml)	X1 Concentration of metals found in paracetamol (µg/ml)	Average	%	X2 Concentration of heavy metals (µg/ml)	X2 Concentration of metals found in paracetamol (µg/ml)	Average	%
Pb	0.01	0.0160	0.0281	2.81	0.01	0.0081	0.0261	2.61
	0.02	0.0271			0.02	0.0221		
	0.03	0.0412			0.03	0.0483		
Ni	0.01	0.0691	0.0462	4.62	0.01	0.0784	0.0491	4.91
	0.02	0.0243			0.02	0.0235		
	0.03	.0452			0.03	0.0456		
Cd	0.01	0.0077	0.0266	2.66	0.01	0.0091	0.0269	2.69
	0.02	0.0312			0.02	0.0226		
	0.03	0.0411			0.03	0.0492		
As	0.01	0.0767	0.0507	5.07	0.01	0.0324	0.0320	3.20
	0.02	0.0342			0.02	0.0285		
	0.03	0.0412			0.03	0.0351		
Hg	0.01	0.0082	0.0263	2.63	0.01	0.0086	0.0256	2.56
	0.02	0.0296			0.02	0.0256		
	0.03	0.0412			0.03	0.0432		

man health in (table 4). Results of new research have shown that the presence of this drug in the body can produce side effects that change a person's perception of risk – a greater risk than being given a placebo. The use of Acetaminophen in patients feels less "negative" emotions because when they are in danger they will not feel as much fear (fear decreases) [22] Toxic metals as impurities are presented in (Table 5), their toxicity should be taken into account, as well as the maximum levels of daily consumption in µg/ml. Graphic representation of heavy metals in paracetamol samples X1, X2 in (Fig. 4).
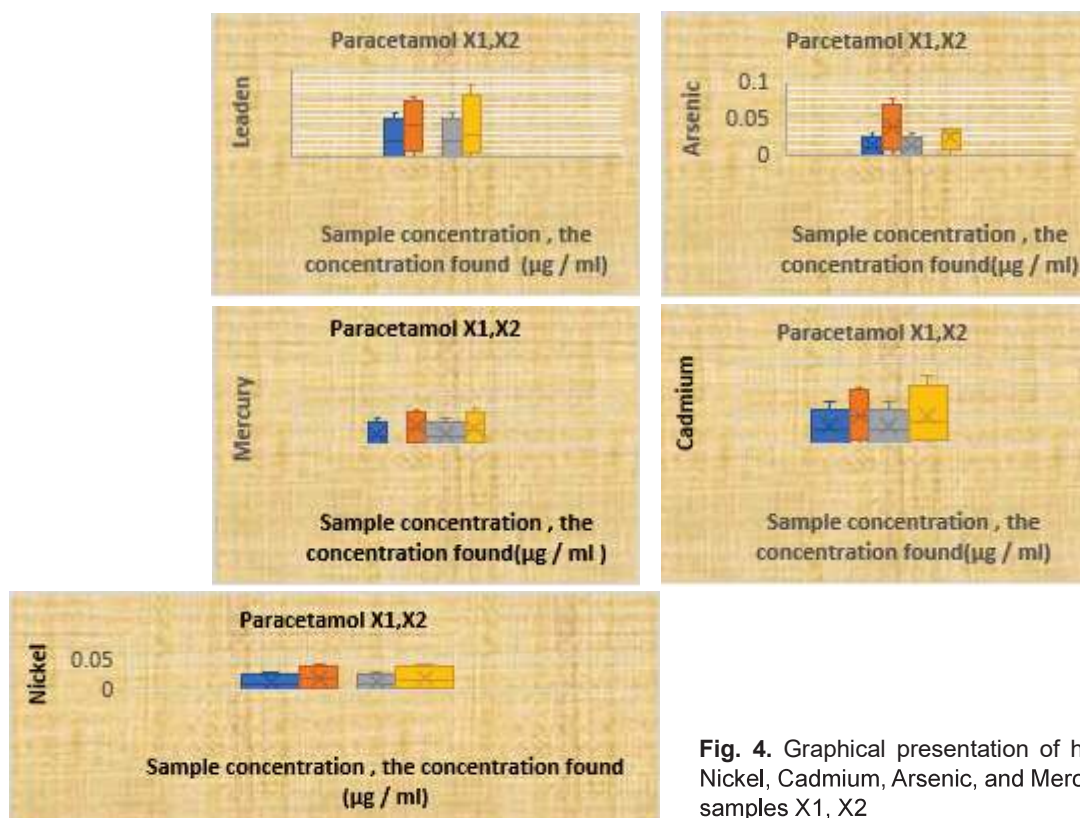

Fig. 4. Graphical presentation of heavy metals (Lead, Nickel, Cadmium, Arsenic, and Mercury), in paracetamol samples X1, X2

Table 5. Validation results for the analysis of Lead, Nickel, Cadmium, Arsenic, and Mercury

Plant	Therapeutic use of medicinal plants	Use of drugs for health treatment	Cultivation or growth of these drugs	Metal concentration (µg/g)									
				Pb	%	Ni	%	Cd	%	As	%	Hg	%
Gentiana lutea	Anti-inflammatory, antiseptic, carminative	Against mucosal and skin inflammations, against flatulence, flatulence, and sedatives	It grows near roads and stony places	0,012	1.2	0,023	2.3	0,011	1.1	0,0056	0.56	0,067	6.7
Juniperus communis	Diuretic, antiseptic, antirheumatic	Helping the urinary organs, improving blood circulation	Everywhere in the lowlands	0,002	0.2	0,043	4.3	0,013	1.3	0,0002	0.2	0,0002	0.2
Hedera helix	Spasmolytic, secretly	Against cough and chronic respiratory infections.	Wooded forests	0,002	0.2	0,043	4.3	0,018	1.8	0,0002	0.2	0,0002	0.2
Vaccinium myrtillus	Antiaretic, antioxidant	It is used as a sedative against coughs, bleeding, and treating the mucous membrane of the throat, and soothing stomach pains.	Subalpine areas	0,028	2.8	0,002	0.2	0,041	4.1	0,0002	0.2	0,0002	0.2
Malva sylvestris	Pain reliever	It has found use in the treatment of the mucous membrane of the mouth, pharynx, throat, pharynx and as a sedative	Roadside	0,032	3.2	0,025	2.5	0,01	1.1	0,0010	0.1	0,0253	2.53
Crataegus monogyna	Cardiotonic	Treatment of heart diseases	Bushy places	0,036	3.6	0,003	0.3	0,014	1.4	0,0010	0.1	0,021	2.1
Althea officinalis	Expectorant	Against coughs, colds, ulcers, inflammation of the mouth, throat, and lungs	It is found (cultivated) in wet places near water channels	0,016	1.6	0,020	2.0	0,015	1.5	0,0023	0.23	0,013	1.3
Matricaria chamomilla	Anti-inflammatory, anti-septic, carminative	Against inflammations of the mucous membrane and skin, against gases, constipation, and sedatives	It grows near stone roads	0,037	3.7	0,031	3,1	0,017	1.7	0.001	0.1	0,047	4.7

DISCUSSION

Based on the analytical (statistical) results of some heavy metals in drugs, the concentration, in some cases, exceeds the maximum allowable values, making these drugs unusable and harmful to human health. The presence of heavy metals in paracetamol poses a more serious problem, particularly affecting the liver (Table 3). Recent research findings have shown that the presence of this drug in the body can lead to side effects that change a person's perception of a greater risk than being given a placebo. Patients using Acetaminophen experience reduced "negative" emotions, because when they are in danger they will not feel as much fear (fear decreases). Toxic metals as impurities are presented in (Table 4), their toxicity should be considered, as well as the maximum daily consumption levels in µg/g. The determination of heavy metals in paracetamol was carried out by atomic absorption spectrometric methods, the results show that the samples in X1 have a high value of Arsenic that varies with the value of 5.07% among other metals, followed by Nickel with values of 4.62. The statistical results show again in the X2 samples that nickel varies with the value of 4.91% and Arsenic with the value of 3.20%, while the concentrations of other analyzed metals remain approximately the same. The study shows that arsenic and nickel are the two metals with the highest concentration in paracetamol compared to other metals. During the production process, the increase in the concentration of metals occurs as a result of impurities in natural raw materials, impurities in reactions, etc. The use of medicinal plants in medicine is extremely large for the treatment of various diseases. Many medicinal plants grow near roads or industrial activities, as these plants often have concentrations of heavy metals in their presence. But for the medicinal plants that are cultivated outside the industrial areas, the results showed that in the medicinal plants such as "Matricaria chamomilla" Lead varies with the value of 3.7% about other plants. The medical plant "Hedera helix" Nickel varies with a value of 4.3%, "Gentiana lutea" varies with a value of 2.3% while Mercury with a value of 4.7% in Table 5. Statistical results in this study on impurities in paracetamol medicinal drugs, medicinal plants have an advantage compared to medicinal drugs.

CONCLUSIONS

Impurities in drugs often have unwanted or toxic effects on human health. Compounds that produce drugs must be careful because the raw materials may be contaminated, the results in this research show in some cases the presence of heavy metals above international parameters or standards.

Nowadays, heavy metals are the main concern for human health. These impurities can either occur naturally or be added as part of the analysis/synthesis of a product. Often impurities can be inadvertently introduced where metal interactions are caused during the manufacturing process. Metallic impurities in drugs can cause serious problems for human health even at very low concentrations. Heavy metals enter the grass chain during the production process, care must also be taken with natural raw materials. Any poison introduced into the system must later be considered injurious to human health even though it relieves the actual symptoms.

Dislocure Summary: The authors have nothing to disclose.

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