Management of the interactions’ risks when using phytomedicines in children

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Abstract: phytomedicines play an essential role in the treatment of children's diseases. Means of plant origin have a better safety profile, and due to the content of biologically active substances, they affect various links of pathological processes. However, data on the safety and efficacy of phytomedicines in children are limited and mostly derived from studies in adults. In addition, there are risks of pharmacokinetic and pharmacodynamic drug interactions. This study aims to study the risks of interaction when using phytomedicines and drugs in children. 100 parents participated in the study, most of whom had 1 or 2 children. An analysis of the pharmacotherapy courses of 50 children was also done. It has been established that parents when choosing medicines for children, consider their origin. Thus, more than 70% of respondents consider phytomedicines to be safer for children and choose them for the treatment of acute respiratory viral infections (73%), diseases of the throat (64%), oral cavity (59%), disorders of the gastrointestinal tract (28%) and others. The phytomedicines of choice were: Chlorophyllip, Sinupret, Wormil Phyto, Proteflazid, Darsil, Cholelesan, etc., which 80% of respondents used in combination with other medicinal products and without a doctor's prescription (75% of respondents). It was revealed that 10% of respondents noted the appearance of undesirable reactions after using phytomedicines, in combination with other medicinal products in children, the manifestations of which were: allergic reactions, digestive disorders, headache/dizziness. Based on the results of the analysis of the pharmacotherapy courses, it was established that the children received an average of 5.8 ± 1.7 medicines. In particular, 28% received 2 or more phytomedicines. In more than 40% of children, the risks of pharmacokinetic interaction of phytomedicines with other medicinal products were revealed. Thus, 10% received herbal remedies based on St. John's wort, which is a CYP3A4 inducer and reduces the effectiveness of albendazole, omeprazole, pantoprazole, and levocetirizine. While more than 30% of children received products based on turmeric, silymarin, or grapefruit extract, which are strong CYP3A4 inhibitors. Risks of pharmacokinetic interaction at the stage of absorption (6% of children) were associated with the use of flax and plantain seeds. In 10% of children, the risk of pharmacodynamic interaction due to the use of thick eucalyptus leaf extract and an antiseptic agent was revealed. Therefore, when using phytomedicines in children, it is necessary to consider the risks of drug interactions. Phytomedicines can affect the pharma-
Macokinetics of other drugs and change the realization of the clinical effect. When choosing and using phytomedicines the interaction of the doctor-pharmacist-parent is essential.

Keywords: Child, Cytochrome P-450 Enzyme Inducers, Cytochrome P-450 Enzyme Inhibitors, Herb-Drug Interactions, herbal medicine, Parents

Introduction
Solving the problem of rational, effective, and safe pharmacotherapy of diseases in children remains an urgent task of today's pharmacy and medicine. It is reported that the prevalence of children's diseases has increased by almost 40% in Ukraine over the past 20 years (Y.G. Antipkin, 2018). The frequency of diabetes, hypertension, and bronchial asthma among children is increasing, which requires new treatment regimens (Zelinska et al., 2021; Volosovets et al., 2020). However, pharmacotherapy in the pediatric population is still usually prescribed empirically on the basis of data obtained in adults. While the physical and physiological characteristics of children are significantly different from adults, which leads to significant differences in the pharmacokinetics and pharmacodynamics of drugs (Bilovol O.M., 2022).

In the treatment of children, phytomedicines are widely used. It is believed that phytomedicines have a number of advantages compared to synthetic drugs. Yes, they have a better safety profile, and due to the content of biologically active substances, they affect various links of pathological processes (Barkat et al., 2020). However, data on the safety and efficiency of phytomedicines in children are limited and mostly received from studies in adults (Polat & Gürol, 2021). In addition, there are risks of pharmacokinetic and pharmacodynamic interactions when using phytomedicines with synthetic drugs (Suroowan & Mahomoodally, 2019; Chrubasik-Hausmann et al., 2018).

Aim
To study the risks of interaction when using phytomedicines and drugs in children.

Materials and methods
A questionnaire survey of parents (n = 100) was carried out regarding the features of choosing and using phytomedicine for children. The questionnaire was formulated in accordance with the methodological recommendations «Organization of sociological surveys of patients/their representatives and medical personnel in health care institu-

Table 1. Characteristics of the respondents’ contingent (n=100)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>n (%)</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>78</td>
</tr>
<tr>
<td>Men</td>
<td>22</td>
</tr>
<tr>
<td><strong>Quantity of children</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
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<td>&gt;3</td>
<td>5</td>
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</table>

Statistical processing of the results was carried out using the program «IBM SPSS Statistics Base version 22.0». The number of observations was analyzed (n), Pearson's chi-squared test ($\chi^2$), and Z-test (Bonferroni correction). The results were considered statistically significant at $p < 0.05$.

Results
Based on the results of the questionnaire survey, it was established that more than 90% of...
respondents pay attention to their origin when choosing medicines for children. In particular, almost 70% of respondents believe that herbal remedies are safer for use in children and choose them for the treatment of acute respiratory viral infections (73%), diseases of the throat (64%), and oral cavity (59%), disorders of the gastrointestinal tract (28%), allergic diseases (15%). To the question: «Who recommended you phytomedicines for children»: almost 70% indicated that the doctor prescribed them, at the same time, 36% used the advice of relatives and acquaintances, 32% – Internet resources, 30% asked the recommendation at pharmacists (Fig. 1).

In general, 75% of the respondents answered that they used phytomedicines for the treatment of children without a doctor’s prescription. Cases of the use of phytomedicines for children without the recommendation of a specialist (doctor/pharmacist) are evidence of irresponsible self-medication, which increases the risks of incorrect use, drug interactions, and, as a result, the appearance of unwanted reactions.

Forward it was investigated which phytomedicines are most often chosen by parents for the treatment of children. More than 60% of respondents used the herbal remedy Chlorophyllipt, which contains an extract of thick eucalyptus leaves and exhibits antiseptic, disinfectant, and anti-inflammatory properties. More than 50% of respondents chose phytomedicines based on echinacea and althea medicinal for children. Almost 55% used Sinupret – a complex herbal remedy. While 42% chose Wormil Fito for the treatment of worm infestations in children. In addition, quite often respondents chose Proteflazid (24%), Darsil (17%), Cholelesan (17%), Gastritol, and valerian extract (14%).

It was found that 80% of respondents used phytomedicines for the treatment of their children in combination with other drugs (Fig. 2), which are: antitussives (75%), antipyretics (73%), antivirals (55%), anthelmintics (37%), antihistamines (25%), which increases the risk of drug interactions.

![Fig. 1. Sources of information for making a decision on the use of phytomedicines in children](image1)
*Note. The response rate is not 100%, as the respondents chose several answers.*

![Fig. 2. Frequency of use of other drug groups when using phytomedicines in children](image2)
*Note. The response rate is not 100%, as the respondents chose several answers.*
According to the results of the survey, there is a high commitment of parents to the use of phytomedicines in children. Thus, almost 20% of the respondents rated the effectiveness of phytomedicines for use in children with 5 points out of 5 possible points, 50% – by 4 points. It is important to note that 10% of respondents observed the appearance of undesirable reactions after the use of phytomedicines, in combination with other drugs in children, which are: allergic reactions (6 cases), digestive disorders (8 cases), headache/dizziness (1 case).

The next step was analysis of the appointment sheets of children who received phytomedicines. It was found that more than half of the children (n = 28) received phytomedicines (Darsil, Karsil, Cholelesan, Chophytol, etc.) that have choleretic and hepatoprotective properties. In addition, 8 children received phytomedicines (Gastritol, Mucofalk, Apetestim, Sakolin, a decoction of flax seeds, etc.) based on medicinal plant raw materials that have gastroprotective properties and help improve digestion. Established that 4 children received phytomedicines that affect urinary tract infections (Urolesan, Cyston). While complex anthelmintic phytomedicine (Wormitel) was taken by 2 children. At the same time, phytomedicines that have antiviral and antimicrobial activity (Chlorophyllipt, Ingalipt), reduce sinus inflammation (Sinupret), and have a calming effect (valerian extract) were prescribed. It was established that 14 children (28%) received 2 or more phytomedicines. In general, there were from 2 to 10 drugs per course of pharmacotherapy (on average 5.8 ± 1.7), which increases the risk of drug interactions. Thus, in more than 40% of children who mostly received 5 or more drugs, the risks of pharmacokinetic interaction of phytomedicines with other drugs were revealed ($\chi^2 = 6.85; \ p < 0.05$).

It was found that 5 children were taking the complex phytomedicine Gastritol (containing extracts of goose foxglove, medicinal chamomile flowers, licorice and degel roots, bitter wormwood, St. John’s wort). Whereas St. John’s wort is a potent inducer of cytochrome P450 enzymes (especially CYP3A4) and glycoprotein P (Nicolussi et al., 2020). The combination of St. John’s wort with albendazole, omeprazole, pantoprazole, and levocetirizine causes reducing their concentration in the blood, and as a result, their effectiveness.

It was established that the pharmacotherapy regimens of 10 children included the herbal remedy Cholelesan (containing extracts of wild carrot fruits, marigold flowers, sand cumin; curcumin C3 complex obtained from the roots of turmeric; oil of turmeric and peppermint). Whereas curcumin is a potent inhibitor of CYP3A4, causes increasing the blood concentration of albendazole, levocetirizine, and pantoprazole, as well as the risk and severity of their adverse reactions. Another important inhibitor of CYP3A4 is silymarin (the active substance of Carsil and Darsil derived from milk thistle extract), which may inhibit the metabolism of vitamins (2 children), doxycycline (2 children) and loratadine (1 child). While 1 child received the complex remedy Detoxyl, which includes grapefruit extract (a CYP3A4 inhibitor), which can suppress the metabolism of doxycycline (Rithaporn та ін. 2007). At the same time, framycetin (the active substance of Isofra) can reduce the rate of excretion and increase the bioavailability of eucalyptus oil, which is part of Ingalipt (1 child) (Bonate et al., 1998).

It should also be noted that the decoction of flax seeds, which was prescribed to 2 children, has an enveloping, astringent, and antacid effect, which can lead to impaired absorption of other drugs (nifuratel, albendazole, esomeprazole). In addition, Mucofalk contains the husk of plantain seeds in its composition, which can impair the absorption of Ascorutin (1 child). To prevent the risk of interaction and influence on the bioavailability of drugs, it is necessary to keep an interval of 2-3 hours between taking a decoction of flax seeds, Mucofalk, and other drugs.

Discussion

The risks of the interaction of phytomedicines and drugs are actively studied in experimental
and clinical studies. Thus, the risks of pharmacodynamic and pharmacodynamic interaction of Scutellaria baicalensis (*Scutellaria baicalensis Georgi*). It has been shown that its biologically active substances (baicalin, baicalein, etc.) have a synergistic interaction with many drugs, which leads to an increase in the effectiveness of pharmacotherapy of infectious diseases, diabetes, and malignant neoplasms. At the same time, the Scutellaria baicalensis affects the pharmacokinetic profile of drugs by changing absorption, distribution, and elimination, as well as by affecting cytochrome P450 enzyme receptors (Zhou et al., 2021). According to the results of in vitro studies, it has been proven that Basil and Protea compacta are CYP1A2 inducers, which affect the metabolism of theophylline, haloperidol, clozapine, etc. In addition, Basil (*Ócimum*) extract may promote CYP2B6 induction. While, Protea compacta (*Protea*) is an inhibitor of glycoprotein P (Amaeze et al., 2021). According to the results of another experimental study, it was established that the simultaneous use of Gastrodia elata and valproic acid reduces the development of resistance to valproic acid and enhances the anticonvulsant effect. The use of Gastrodia elata also had a neuroprotective effect on the hippocampus (Yang & Tsai, 2022).

S. Suroowan and M. Mahomoodally published the results of the analysis, which included almost 200 scientific publications, regarding the risks of the phytomedicines’ interaction. Thus, Ginkgo biloba is an inducer of both CYP2C9 and CYP3A4, which leads to changes in the bioavailability of many drugs, including midazolam, nifedipine, and lopinavir. Whereas Ginseng (*Pánax*) activates CYP2C9, reducing the anticoagulant activity of warfarin. It has been established that Camellia sinensis increases the bioavailability and risk of toxic reactions of buspirone. Glycyrrhiza glabra may increase the metabolism of calcium channel blockers (nifedipine, verapamil, and diltiazem). It is reported that phytomedicines, due to their effect on hepatocytes, can have a hepatotoxic effect. The authors of the review emphasize the importance of controlling the use of phytomedicine in combination with drugs that have a low therapeutic index (Suroowan & Mahomoodally, 2019).

Thus, phytomedicines contain biologically active compounds and can interact with drugs, including prescription drugs, affecting their effectiveness and safety profile. When using phytomedicines in children, it is important to inform doctors and parents about drug interactions and to provide recommendations on the correct use of phytomedicines, to reduce the risk of dangerous drug interactions. When choosing phytomedicines for children, an important aspect is the interaction between the doctor and the pharmacist.

**Conclusions**

1. It was established that more than 70% of the surveyed parents consider phytomedicines safe for use in children and often use them without a doctor’s prescription.

2. It has been demonstrated that 80% of respondents use phytomedicines for children in combination with other drugs, which increases the risks of interaction.

3. According to the results of the analysis of pharmacotherapy courses, in more than 40% of children, risks of the interaction of phytomedicines and other medicines were revealed, which were mainly associated with the use of inducers (St. John’s wort, etc.) and inhibitors of metabolism (turmeric, silymarin, etc.), absorption disorders (flax seeds and plantain) medicinal products.

4. To ensure the rational use of phytomedicines in children, and to prevent risks of interaction, teamwork between the doctor-pharmacist and parents is important. Thus, a pharmacist implements special knowledge of clinical pharmacology regarding the regimen of drug use, features of their interaction, and prevention of unwanted reactions.

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**Conflict of interest**

The authors have no conflict of interest to declare.

**Consent to publication**

The authors have read and approved the final version of the manuscript. The authors agreed to publish this manuscript.

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REFERENCES


Менеджмент ризиків взаємодії при застосуванні фітозасобів у дітей

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Анотація: Важливу роль у лікуванні захворювань дітей відіграють фітозасоби. Засоби рослинного походження мають кращий профіль безпеки, а завдяки вмісту біологічно активних речовин впливають на різні ланки патологічних процесів. Разом з тим, існують ризики фармакокінетичної та фармакодинамічної взаємодії. Встановлено, що 10% респондентів після застосування фітозасобів у комплексі з іншими лікарськими засобами відмічали небажані реакції, проявами яких були: ентерогастроенкіальні реакції (15%), алергічні реакції (10%), головний біль/запаморочення. За результатами аналізу курсів фармакотерапії встановлено, що діти в середньому отримували 5,8 ± 1,7 лікарських засобів. Зокрема, 28% отримували засоби на основі звіробою продірявленого, що є індуктором CY-

Під час вживання фітозасобів слід враховувати можливість вибору фітозасобів з іншим профілем активності та ефективності, враховуючи можливість виникнення небажаних реакцій. При виборі та застосуванні фітозасобів важливою є взаємодія лікар-фармацевт-батьки.

Ключові слова: батьки, діти, взаємодія рослин та лікарських засобів, індуктори ферментів цитохрому Р-450, інгібітори ферментів цитохрому Р-450, фітозасоби.

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