



# Potential pharmacokinetic and pharmacodynamic herb–drug interactions of *Andrographis paniculata* (Burm. f.) and andrographolide: A systematic review

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## ABSTRACT

**Introduction:** Herb–drug interactions (HDIs) in pharmacokinetics and pharmacodynamics can occur when natural compounds are used in combination with drugs. This study aimed to review the potential interaction of *Andrographis paniculata* (Burm. f.) extract (APE) and its primary compound andrographolide (AND) with several drugs exhibiting various pharmacological activities.

**Methods:** In this systematic review, articles were collected from international databases such as PubMed, Science Direct, Springer Link, and Scopus until August 2021. The following keywords were used: *Andrographis paniculata*, andrographolide, HDI, drug interaction, pharmacokinetics, and pharmacology. This review was written in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), SYRCLE's risk of bias (RoB) tool for animal intervention studies, and Cochrane RoB 2 tool to analyze the RoB for qualitative assessment.

**Results:** Twelve articles were included in accordance with the inclusion and exclusion criteria of this study. Five studies explored the potential of HDIs for combining APE with drugs and AND with theophylline, etoricoxib, nabumetone, naproxen, and tolbutamide. Five studies focused on AND in combination with aminophylline and doxofylline, meloxicam, glyburide, glimepiride, metformin, and warfarin. Two studies tested the combination of APE with gliclazide and midazolam. The HDI mechanism involving the inhibition or induction of cytochrome P450 enzyme expression was dominant in influencing the drug's pharmacokinetic profile. Pharmacological studies on the combination of several drugs, particularly anti-inflammatory and antidiabetic drugs, showed a synergistic activity.

**Conclusion:** APE and AND have potential pharmacokinetic and pharmacodynamic HDIs with various drugs. This study can be used as a therapeutic consideration in clinical aspects related to the possibility of HDIs of *A. paniculata* (Burm. f.).

### *Implication for health policy/practice/research/medical education:*

*Andrographis paniculata* (Burm. f.) and andrographolide have the potential to cause pharmacokinetic and pharmacodynamic interactions with several commonly used drugs. This systematic review explains these potential HDIs, which may be taken into consideration in future clinical studies and therapies involving these drugs.

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## Introduction

Herb–drug interactions (HDIs) are drug-related problems in therapy because they can cause therapeutic failures that are difficult to identify. The lack of reports on patients

using drugs concurrently with herbal medicines and the inability of health workers to identify the emergence of potential and clinically relevant HDIs contribute to these problems (1,2). Strategies that deal with HDIs cases

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in clinical practice are often inappropriate because the sources of information related to HDIs that can be used as a guide in therapy are limited. The type and composition of herbal medicines commonly used by patients are also poorly described (3). The most widely reported cases of the emergence of HDIs today are the modulation of herbal medicinal components in the drug metabolism system involving cytochrome P450 (CYP)-metabolizing enzymes (4).

Chemical compounds in herbal medicines can act as reversible inhibitors, irreversible inhibitors, or inducers of the CYP enzyme; they alter the pharmacokinetic profiles of drugs and cause an increase or decrease in drug levels in plasma, tissues, and urine (5). Previous reviews found that HDIs in the pharmacokinetic phase are the most prevalent, accounting for more than 90% of the total cases, including supported and unsupported case reports (3). HDI-induced changes in a drug's pharmacokinetic profile can affect drug levels in the blood and the amount of drug binding to a target action/receptor, which can increase or decrease the effectiveness of its therapy because of the emergence of HDI mechanisms in the pharmacodynamic phase in the form of additive, synergistic, or antagonistic effects on pharmacological activity (6).

HDIs may occur in therapy because of the extensive use of herbal medicines from plants as a complementary therapy to overcome a particular disease. For instance, *Andrographis paniculata* (Burm. f.) is a plant widely used in disease therapy in several countries and regions, such as Thailand, China, Bangladesh, Japan, Malaysia, Scandinavia, Indonesia, India, Britain, and the Philippines. This plant elicits pharmacological effects, including analgesia, anti-inflammation, antimalaria, antiviral, antibacterial, immunosuppression, hepatoprotection, antidiabetes, anti-obesity, antioxidation, antifertility, and anticancer, which have been proven both *in vitro* and *in vivo* (7-10). Andrographolide (AND) and its derivatives, such as neoandrographolide, 14-deoxyandrographolide, and 14-deoxy-11,12-didehydro-andrographolide, have been identified as secondary metabolites of *A. paniculata*. AND plays a role in determining the pharmacological activity of *A. paniculata* (9,11,12). This plant is widely used for therapy in traditional and herbal medicinal preparations developed in various countries because of the numerous pharmacological activities of *A. paniculata* and AND.

*Andrographis paniculata* and AND influence the expression and activity of several CYP enzyme families. Both reduce the mRNA expression of CYP2C in rat hepatocytes in primary culture and the mRNA expression and activities of CYP3A in human hepatocytes in primary culture (13). Conversely, AND increases the mRNA expression of CYP450 family enzymes (CYP1A1, CYP1A2, CYP2A4, CYP1B1, CYP2B9, and CYP2B9) in several mouse/rat hepatocytes in primary cultures (14-18). AND also decreases the mRNA expression levels

of CYP1A2, CYP2D6, and CYP3A4 in HepG2 cells and the mRNA expression of CYP3A in Caco-2 cells (19,20). *A. paniculata* and AND affect the activities of human hepatic CYPs, such as CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (13,21,22). Therefore, these findings can be used as a basis for predicting the possible occurrence of HDIs, especially for drugs whose metabolism mainly involves CYP enzymes.

This review aimed to present the interaction mechanisms of *A. paniculata* and AND with several drugs by exploring the following interaction mechanisms: pharmacokinetics, including the absorption, distribution, metabolism, and excretion (ADME) phase, and pharmacodynamics, including pharmacological activities. Thus, this review could provide insights into preventing and overcoming potential HDIs.

## Methods

### Study protocol

This study was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (24).

### Search strategy

All related studies published until August 2021 were systematically searched from PubMed, Science Direct, Springer Link, and Scopus with the following keywords: *Andrographis paniculata*, andrographolide, herb-drug interaction, drug interaction, pharmacokinetic, and pharmacology. MESH terms were also used (Herb–drug interaction [MESH Terms]) AND pharmacokinetic) OR Pharmacodynamic) AND *Andrographis paniculata* (Burm. f.) AND andrographolide) for PubMed.

### Inclusion criteria

Studies were included if they satisfied the following criteria: experimental studies or clinical trials, randomization in studies, and original English articles on the evaluation of potential pharmacokinetic and/or pharmacodynamic interactions of the combination of *A. paniculata* or AND with drugs.

### Exclusion criteria

Studies were excluded if they met the following criteria: literature review, systematic review articles, conference articles, letters/editorials, cases, theses, and other irrelevant studies; absence of proper sampling methods in studies; and pharmacokinetic and pharmacodynamic combination studies other than experimental studies on animal or human clinical trials (*in silico* or *in vitro*).

### Selection of studies and data extraction

This review was performed on each article in accordance with the inclusion and exclusion criteria. A checklist was used as a basis for determining the quality of each article. The checklist was composed of the author's name,

publication year, study type, drug type, herbal sample type, dose, administration route, pharmacokinetic profile, and pharmacological activity test. A flow chart was then created in accordance with the PRISMA guidelines to report the systematic review process (Figure 1). The obtained preclinical study articles were analyzed in terms of their risk of bias (RoB) by using SYRCLE, which is a tool used to assess the quality of specific assays in animal studies (24). For the clinical study, the RoB was examined with the Cochrane RoB 2 tool for randomized crossover trials according to the type of study obtained in this systematic review (25).

## Results

In the early stages of searching for articles in several databases, 139 titles were obtained. After the selection by two authors, nine duplications were found, and 116 studies were excluded because they did not meet the inclusion criteria: not relevant studies ( $n = 103$ ); review articles ( $n = 12$ ); and other than *in vivo* studies ( $n = 1$ ). A total of 18 studies successfully passed the initial screening stage and followed the topics determined by the authors. However, four studies did not meet the inclusion criteria after the titles and abstracts were screened. After 14 studies were obtained, 1 study did not include pharmacokinetic profile data, and 1 study was a sample test of herbal preparations, which were the standardized fixed combinations of extracts from *A. paniculata* and *Eleutherococcus senticosus*. Thus, 12 studies were obtained, which were declared to meet all the criteria determined through data extraction

(Figure 1).

Five studies focused on HDIs from the combination of *A. paniculata* extract (APE) with the theophylline, etoricoxib, naproxen, tolbutamide, and midazolam, and the combination of AND with theophylline, etoricoxib, nabumetone, naproxen, and tolbutamide. Five studies only involved HDIs of the combination of AND and other drugs (aminophylline and doxofylline, meloxicam, glyburide, glimepiride, metformin, and warfarin). Two studies explored the combinations of APE with gliclazide and midazolam. Afterward, all 12 HDI studies on the pharmacokinetics were examined and compared in terms of pharmacokinetic parameter values for single and combination medication therapy with APE or AND. Five studies did not analyze HDIs during the pharmacodynamic phase and did not continue the analysis of the HDI mechanism by measuring the pharmacological activity of single and combination treatments. However, the possibility of HDIs could still be predicted by comparing the reported changes in pharmacokinetic parameters. After the qualitative assessment of the RoB via SYRCLE from articles used in a systematic review, the results indicated that several studies, especially those involving randomization in animal housing, randomization in sampling, and researcher blinding, could be categorized under a high RoB (Table 1).

A study used a combination of low and high doses to explore HDIs between APE and AND with a bronchodilator drug, namely, theophylline, in animals. In particular, theophylline concentrations in the blood

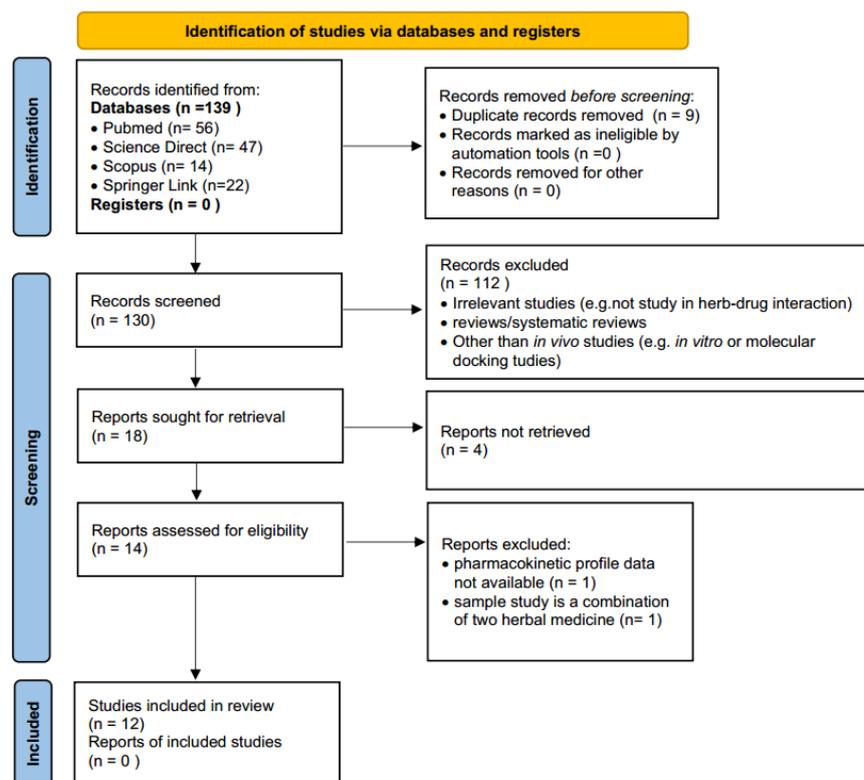


Figure 1. Flowchart of the study.

**Table 1.** Risk of bias of studies examined with the SYRCLE of the bias tool for animal studies

| Study                     | 1                | 2                | 3                | 4                  | 5                  | 6                | 7                | 8              | 9              | 10                   |
|---------------------------|------------------|------------------|------------------|--------------------|--------------------|------------------|------------------|----------------|----------------|----------------------|
|                           | Selection bias 1 | Selection bias 2 | Selection bias 3 | Performance bias 1 | Performance bias 2 | Detection bias 1 | Detection bias 2 | Attrition bias | Reporting bias | Other potential bias |
| Chien et al (26)          | ✓                | ✓                | ✓                | ?                  | ?                  | x                | ?                | ?              | ✓              | ✓                    |
| Li et al (27)             | ✓                | ✓                | ✓                | ?                  | ?                  | x                | ?                | ✓              | ✓              | ✓                    |
| Balap et al (28)          | ✓                | ✓                | ✓                | ?                  | ?                  | ?                | ✓                | ✓              | ✓              | ✓                    |
| Balap et al (30)          | ✓                | ✓                | ✓                | ?                  | ?                  | ?                | ✓                | ✓              | ✓              | ✓                    |
| Balap et al. (29)         | ✓                | ✓                | ✓                | ?                  | ?                  | ?                | ✓                | ✓              | ✓              | ✓                    |
| Vaishali et al (31)       | ?                | ✓                | ✓                | x                  | ?                  | x                | ✓                | ✓              | ✓              | ?                    |
| Chen et al (32)           | ✓                | ✓                | ?                | ?                  | ?                  | ?                | ?                | ✓              | ✓              | ✓                    |
| Samala dan Veeresham (34) | ✓                | ✓                | ?                | ?                  | ?                  | ?                | ?                | ✓              | ✓              | ?                    |
| Mouid (33)                | ✓                | ✓                | ✓                | ?                  | ?                  | ?                | ✓                | ✓              | ✓              | ✓                    |
| Samala dan Veeresham (35) | ✓                | ✓                | ✓                | ?                  | ?                  | ?                | ✓                | ✓              | ✓              | ✓                    |
| Zhang et al (36)          | ?                | ✓                | ?                | ?                  | ?                  | ?                | ✓                | ✓              | ✓              | ?                    |

(✓) Yes: indicates a low risk of bias

(x) No: indicates a high risk of bias

(?) Unclear: indicates an unclear risk of bias

of experimental animals without treatment and with APE and AND for 3 days at low and high doses were analyzed with HPLC/UV instruments on day 4. Based on these data, the pharmacokinetic parameters were compared between single and combination treatments. This study showed that the most significant changes in pharmacokinetic parameters included the increased CL and the decreased AUC values in the low-dose theophylline group with APE and AND pretreatment. At high theophylline doses,  $T_{1/2}$  and MRT significantly decreased by 14% and 17%, respectively (26). Several pharmacokinetic parameters changed throughout the study, indicating that the quantity and duration of time the medication remained in the bloodstream of the test animal decreased. It is hypothesized that changes in the concentration of theophylline in the blood, as determined by the values of these pharmacokinetic parameters, would reduce the pharmacological impact of theophylline.

Studies on the HDIs of other bronchodilator drugs, especially in combination with AND, focused on aminophylline and doxofylline. In these studies, test animals were divided into several groups (individual administration of aminophylline, combination of AND and aminophylline, individual administration of doxofylline, and combination of AND and doxofylline). The AND group was pretreated for 4 days; on day 5, they were given aminophylline and doxofylline. Among the pharmacokinetic parameters of aminophylline combined with AND, the AUC value had the most significant increase. For doxofylline, AUC,  $T_{1/2}$ , and  $C_{max}$  increased, but this increase was not significant compared with those of the single treatment group (27). AUC and  $C_{max}$  increased in this research, indicating an increase in aminophylline and doxofylline's blood concentration, which might promote drug distribution and binding to the target of action. Furthermore, AND prolonged the elimination half-life of doxofylline, extending the drug's lifetime in the body. The elevation in blood drug concentration in medications with a narrow therapeutic index, such as aminophylline and doxofylline, should be highlighted even though the increase in these parameters was not statistically significant.

Studies were performed on several anti-inflammatory drugs, including etoricoxib, nabumetone, naproxen, and meloxicam, in terms of their HDIs between APE and AND. APE, AND, and etoricoxib were used to determine their pharmacokinetic parameters, which were then compared with a single etoricoxib treatment. Their results revealed that several pharmacokinetic parameters of etoricoxib combination treatment significantly varied (28). These results were also consistent with those of studies on HDIs with naproxen. Several pharmacokinetic parameters of naproxen decreased after it was combined with APE and AND ( $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ ), but Vd increased significantly. A previous study examined the anti-arthritic activity by evaluating the paw volume, mechanical hyperalgesia,

nociceptive threshold, histopathology of inflamed joints, and histopathological representation of tibiotarsal joints after the administration of a combination of APE and AND with etoricoxib and naproxen; the results showed a significant synergistic anti-arthritic activity (28,29). The decrease in etoricoxib and naproxen blood levels correlated with the increase in the volume of distribution, indicating that the medication concentration was high in the targeted site. Increased drug distribution to the target of action is essential to encourage pharmacological effects. APE and AND also have anti-inflammatory properties. The combined treatment has a synergistic impact.

By contrast, another study on HDIs with nabumetone via a pharmacodynamics assay showed that the anti-arthritic activity significantly decreased; similarly, several pharmacokinetic profiles ( $C_{max}$ , AUC, and  $T_{1/2}$ ) decreased (30). The reduction in some of these pharmacokinetic parameters was not supported by a statistically significant increase in volume distribution. This combination did not have a synergistic effect because the drug concentration at the targeted site did not enhance. Studies on the HDIs of meloxicam also demonstrated the significant effect of the combination of this drug with AND on several pharmacokinetic parameters (31).

Studies on the HDIs of the combination of APE and AND with several oral antidiabetic drugs revealed mixed results. The administration of APE and AND could enhance the antihyperglycemic effect of glyburide and the glucose-lowering effect of glimepiride and metformin. Conversely, this treatment did not influence the hypoglycemic effect of tolbutamide. The increase in the pharmacological effect of the combination of APE and AND with oral antidiabetics was supported by changes in pharmacokinetic parameters. For instance,  $C_{max}$ , AUC, and  $T_{1/2}$  significantly decreased, and CL and Vd of glyburide, gliclazide, glimepiride, and metformin increased. By contrast, AUC,  $C_{max}$ ,  $T_{max}$ , and MRT of tolbutamide decreased, but its Vd and CL were not reported (32–35).  $T_{max}$  values for glyburide, glimepiride, and metformin were not different, indicating that APE or AND did not influence absorption rate. Rather than drug displacement chemicals in APE or AND, an inhibitory effect on drug metabolic pathways may have been related to the observed increase in  $C_{max}$  and AUC followed by a reduction in Vd values. Because of the existence of HDIs throughout the metabolic phase, the inhibitory effect on the drug-metabolizing enzymes may influence the increasing pharmacological effects of the drugs.

In a previous study, the level of warfarin was reduced by the co-administration of AND for 7 days, and this treatment was analyzed on day 8 through LC-MS/MS. The pharmacokinetic parameters of this co-administration significantly changed, which likely caused HDIs (36). Several pharmacokinetic parameters were observed to be altered in this study. It is certainly possible that the activity of AND on warfarin metabolizing enzymes had an essential role. A clinical trial involving the HDIs of

APE with the anticonvulsant drug midazolam in healthy volunteers. The results showed that the CYP3A4 inhibitor activity of APE and changes in the pharmacokinetic parameters of midazolam were not clinically significant although they reduced the blood pressure and pulse rate (37). Through its inhibition of the CYP3A4 enzyme, APE influences how much drug is absorbed and circulated in the body.

## Discussion

Studies on the mechanism of herb–drug interactions are complicated and full of challenges. The compound composition should be considered to predict the specific compounds in these natural materials that play an important role in the interaction mechanism. Furthermore, if the medicinal herb sample is a secondary metabolite-rich extract or if the herbal preparation includes more than one plant, the sample should be tested. The mechanism of HDIs was studied in this review based on preclinical studies and clinical trials involving APE and AND with several therapeutic drugs in terms of their pharmacokinetic and pharmacodynamic characteristics.

The pharmacokinetic parameters of drugs in HDIs change, and these values can be measured to describe the variations in the ADME of drugs. The most common mechanism underlying pharmacokinetic interactions is the drug-mediated inhibition and induction of drug-metabolizing CYP isozymes (4,38). Therefore, *in vitro* studies on the inhibition or induction of the expression and activity of the CYP family of enzymes can be conducted to assess potential drug interactions (1,3,38).

The pharmacokinetic parameters of various drugs, such as theophylline, aminophylline, and doxophylline, for treating asthma and chronic obstructive pulmonary disease change because of APE and AND pretreatment (Table 2). Changes in the expression and performance of CYP1A2, CYP2E1, and CYP3A4 enzymes that metabolize these drugs can increase or decrease the pharmacokinetic profile (39,40). APE and AND can alter the pharmacokinetic parameters of theophylline in the blood because of their effects on the CYP1A2 enzyme (16,41). APE and AND can act as CYP1A2 substrates, increasing theophylline metabolism, as evidenced by changes in pharmacokinetic parameters, such as decreased  $C_{max}$  and AUC. They also can significantly increase elimination parameters that affect blood theophylline levels (26). Reduced drug concentrations in the body may have a detrimental effect on the pharmacological activities of the drug by reducing the number of free drugs that bind to the target of action. Additionally, the impact on enhanced drug metabolism may reduce the intensity and duration of the therapeutic activity (2,42).

The combination of AND with aminophylline and doxophylline did not significantly alter pharmacokinetic parameters. However, no further research on the effect of this combination on pharmacodynamic aspects was

conducted. The administration route should also be considered because all three drugs were administered via intravenous injection in this study. As a result, interactions likely occur during metabolism and excretion. This study also revealed that the effects of aminophylline and doxophylline were lower than that of theophylline. They also controlled blood drug levels and unchanged drug pharmacokinetic parameters. These findings suggest that doxophylline is safer than aminophylline and theophylline when they are combined with AND. Some non-linear pharmacokinetic data on theophylline in the presence of APE treatment predict the effects of APE components other than AND, which can inhibit elimination and cause the accumulation of theophylline in the blood (26). Theophylline, aminophylline, and doxophylline have narrow therapeutic indices (43). Due to variations in several pharmacokinetic parameters, the therapeutic concentrations of these drugs might alter to subtherapeutic or toxic levels (44,45). As a possible consequence, this problem must be recognized, and further research into the effect of alterations in pharmacokinetic parameters on pharmacological effects is required.

The pharmacokinetic interaction mechanism involving the CYP1A2 enzyme from APE and AND has also been proven in several anti-inflammatory drugs, such as etoricoxib, nabumetone, and naproxen (28–30). These drugs are metabolized primarily through the CYP1A2 enzyme activity pathway in mice and other enzymes, such as CYP2A6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, expressed in humans (46–49).  $C_{max}$  and AUC of etoricoxib and naproxen decrease significantly, indicating that their blood levels decrease because of the administration of APE and AND, which are predicted to induce CYP1A2 enzymes. From a pharmacodynamic standpoint, the decrease in etoricoxib and naproxen levels is beneficial because they have synergistic effects when they are combined with APE and AND. The study demonstrated that reducing a drug's blood concentration does not invariably result in decreased activity; this may be due to the drug's broad therapeutic index (50,51). In this case, the pharmacodynamic interaction is significant since APE and AND both have a very potent anti-inflammatory activity, which results in a synergistic effect.

Based on anti-arthritis test parameters and histopathological evaluation, their synergistic effect can occur in the presence of a better pharmacological effect than the single treatment. Such a synergistic effect is inextricably linked to the anti-inflammatory activity of APE and AND. APE exhibits anti-inflammatory activity by suppressing the production of cytokines and chemokines, such as IL-1, IL-6, CXCL-1, MCP-1, and RANTE, through the inhibition of the NF- $\kappa$ B signal pathway (52). AND also has anti-inflammatory activity by inhibiting NF- $\kappa$ B activation (53,54). It prevents human neutrophils from producing oxygen radicals (55). Furthermore, it inhibits and reduces COX-2 expression in HL60/neutrophils

**Table 2.** Studies on the herb-drug interactions of *Andrographis paniculata* (Burm. f.) and andrographolide with drugs

| Drug category     | Drugs        | Dose of drugs | Compounds    | Dose   | Administration                                       | Sample study   | Pharmacokinetic profiles  |   | Pharmacodynamic effect                          | References |
|-------------------|--------------|---------------|--------------|--|--|--|---|---|---|------------|
|                   |              |               |              |  |  |  | Increased   | Decreased   |   |            |
| Bronchodilator    | Theophylline | 1 mg/kg BW    | APE          | 1000 mg/kg BW                                    | APE gastrogavage;<br>theophylline iv injection       | Male Sprague Dawley rats                                       | Vd, MRT, CL*  | C <sub>max</sub> , AUC*, T <sub>1/2</sub> β, MRT  | NM  | (26)       |
|                   |              |               | AND          | 77 mg/kg BW                                      |  |  | C <sub>max</sub> , Vd, CL*  | AUC*, Vd, T <sub>1/2</sub> α, T <sub>1/2</sub> β, MRT   |   |            |
|                   |              |               | APE          | 2000 mg/kg BW                                    |  |  | Vd, T <sub>1/2</sub> α, CL*   | C <sub>max</sub> , AUC*, T <sub>1/2</sub> β, MRT  |   |            |
|                   |              |               | AND          | 154 mg/kg BW                                     |  |  | CL*   | C <sub>max</sub> , AUC*, Vd, T <sub>1/2</sub> β, MRT  |   |            |
|                   |              | 5 mg/kg BW    | APE          | 1000 mg/kg BW                                    | AUC, Vd, T <sub>1/2</sub> α, T <sub>1/2</sub> β, MRT | C <sub>max</sub> , CL*   |   |   |   |            |
|                   |              |               | AND          | 77 mg/kg BW                                      | C <sub>max</sub> , CL                                | AUC, Vd, T <sub>1/2</sub> α, T <sub>1/2</sub> β*, MRT*         |   |   |   |            |
| Aminophylline     | 20 mg/kg BW  | AND           | 100 mg/kg BW | AND orally;<br>aminophylline iv injection        | Male Sprague Dawley rats                             | AUC <sub>0-t</sub> *, MRT, T <sub>1/2</sub> , T <sub>max</sub> | CL, C <sub>max</sub>  | NM  | (27)  |            |
|                   | Doxofylline  | 30 mg/kg BW   | AND          | 100 mg/kg BW                                     |  | AND orally<br>doxofylline iv injection                         | AUC <sub>0-t</sub> , T <sub>1/2</sub> , T <sub>max</sub>            | MRT, CL, T <sub>max</sub>   |   | NM         |
| Anti-inflammatory | Etoricoxib   | 10 mg/kg BW   | APE          | 200 mg/kg BW                                     | Orally   | Female Wistar rats   | T <sub>max</sub> , CL*, Vd*, AUMC <sub>0-∞</sub>                    | C <sub>max</sub> *, AUC <sub>0-t</sub> *, AUC <sub>0-∞</sub> *, AUMC <sub>0-t</sub> *, MRT <sub>0-t</sub> *, MRT <sub>0-∞</sub> *, T <sub>1/2</sub> * | Significant synergistic anti-arthritis activity | (28)       |
|                   |              |               | AND          | 60 mg/kg BW                                      |  |  | CL*, Vd*, AUMC <sub>0-∞</sub>                                       | C <sub>max</sub> *, AUC <sub>0-t</sub> *, AUC <sub>0-∞</sub> *, AUMC <sub>0-t</sub> *, MRT <sub>0-t</sub> , MRT <sub>0-∞</sub> , T <sub>1/2</sub> *   |   |            |
|                   | Nabumetone   | 7.5 mg/kg BW  | APE          | 200 mg/kg BW                                     | Orally   | Male albino Wistar rats  | T <sub>1/2</sub> *, MRT <sub>0-t</sub> , Vd, CL, MRT <sub>0-∞</sub> | C <sub>max</sub> *, T <sub>max</sub> *, AUC <sub>0-t</sub> , AUC <sub>0-∞</sub>   | Significant decrease in anti-arthritis activity | (30)       |
|                   |              |               | AND          | 60 mg/kg BW                                      |  |  | T <sub>max</sub> , CL   | C <sub>max</sub> *, T <sub>1/2</sub> *, MRT <sub>0-t</sub> , Vd, AUC <sub>0-t</sub> , AUC <sub>0-∞</sub> , MRT <sub>0-∞</sub>                         |   |            |
|                   | Naproxen     | 7.5 mg/kg BW  | APE          | 200 mg/kg BW                                     | Orally   | Male albino Wistar rats  | MRT <sub>0-t</sub> , MRT <sub>0-∞</sub> , Vd*, CL                   | C <sub>max</sub> *, T <sub>max</sub> *, AUC <sub>0-t</sub> , AUC <sub>0-∞</sub> , T <sub>1/2</sub>  | Significant synergistic anti-arthritis activity | (29)       |
|                   |              |               | AND          | 60 mg/kg BW                                      |  |  | AUC <sub>0-∞</sub> , MRT <sub>0-∞</sub> , Vd*                       | C <sub>max</sub> *, T <sub>max</sub> *, AUC <sub>0-t</sub> , T <sub>1/2</sub> , MRT <sub>0-t</sub> , CL   |   |            |
| Meloxicam         | 5 mg/kg BW   | AND           | 50 mg/kg BW  | AND orally;<br>meloxicam intramuscular injection | Male albino Wistar rats                              | T <sub>1/2</sub> α*, AUC <sub>0-∞</sub> *, AUMC                | C <sub>max</sub> *, T <sub>1/2</sub> β, Vd, MRT                     | NM  | (31)  |            |

Table 2. Contiued

| Drug category  | Drugs        | Dose of drugs | Compounds    | Dose  | Administration | Sample study             | Pharmacokinetic profiles   |   | Pharmacodynamic effect                                 | References |
|----------------|--------------|---------------|--------------|---|----------------|--------------------------|--|---|--|------------|
|                |              |               |              |   |                |                          | Increased  | Decreased   |  |            |
| Antidiabetic   | Tolbutamide  | 20 mg/kg      | APE          | 2 g/kg BW   | Orally         | Male Sprague Dawley rats | -  | AUC <sub>0-12h</sub> *, T <sub>max</sub> *, C <sub>max</sub> *, T½ β, Vd, MRT | Does not impair the hypoglycemic effect of tolbutamide | (32)       |
|                |              |               | AND          | 50 mg/kg BW   |                |                          | MRT  | AUC <sub>0-12h</sub> *, T <sub>max</sub> *, C <sub>max</sub> *, T½ β, Vd      |  |            |
|                | Glyburide    | 10 mg/kg BW   | AND          | 4.5 mg/kg BW  | Orally         | Male albino Wistar rats  | C <sub>max</sub> *, AUC <sub>0-t</sub> *, AUC <sub>0-∞</sub> *, T½, MRT                                      | CL*, Vd*  | Enhances the antihyperglycemic effect                  | (34)       |
|                | Gliclazide   | 2 mg/kg BW    | APE          | 2000 mg/kg BW   | Orally         | Male albino Wistar rats  | C <sub>max</sub> *, T <sub>max</sub> *, T½*, AUC <sub>0-∞</sub> *, AUMC <sub>0-∞</sub> *, MRT <sub>0-∞</sub> | Vd, CL  | NM   | (33)       |
|                | Glimepiride  | 1 mg/kg BW    | AND          | 4.5 mg/kg BW  | Orally         | Male albino Wistar rats  | C <sub>max</sub> *, AUC <sub>0-t</sub> *, AUC <sub>0-∞</sub> *, T½*, MRT                                     | CL*, Vd*  | Enhances the glucose-lowering effect                   | (35)       |
| Metformin      | 100 mg/kg BW | AND           | 4.5 mg/kg BW | C <sub>max</sub> *, AUC <sub>0-t</sub> *, AUC <sub>0-∞</sub> *, T½* |                |                          | CL*, Vd*   | Enhances the glucose-lowering effect  |  |            |
| Anticoagulant  | Warfarin     | 0.5 mg/kg BW  | AND          | 30 mg/kg BW   | Orally         | Male Sprague Dawley rats | C <sub>max</sub> *, T½, AUC <sub>0-∞</sub> *, MRT  | T <sub>max</sub> *  | NM   | (36)       |
| Anticonvulsant | Midazolam    | 7.5 mg        | APE          | 1000 mg   | Orally         | Healthy male volunteers  | AUC <sub>0-12h</sub> *, AUC <sub>0-∞</sub>   | C <sub>max</sub>  | Effect in lowering blood pressure and pulse rate       | (37)       |

NM: not mentioned; APE: *Andrographis paniculata* (Burm. f.) extract; AND: andrographolide; AUC: area under the plasma drug concentration curve; C<sub>max</sub>: maximum plasma drug concentration; T<sub>max</sub>: time to achieve C<sub>max</sub>; MRT: mean resident time; CL: clearance, Vd: apparent volume of distribution; T½: half-life is the time required to produce a 50% reduction in blood or plasma concentration; T½α: half-life of the distribution phase; and T½β: half-life of the elimination phase.

\* Significantly changed pharmacokinetic parameter values.

induced by platelet-activating factor and N-formyl-methionyl-leucyl-phenylalanine (56).

The combination of APE and AND with other anti-inflammatory drugs, such as nabumetone and meloxicam, shows some changes in the pharmacokinetic profile. The decrease in the pharmacologically active metabolite 6-MNA of nabumetone in the blood is measured in the presence of a decrease in  $C_{max}$  and AUC (30). This decrease affects pharmacodynamic aspects, resulting in a reduction in the anti-arthritic effect of nabumetone. Therefore, further human studies should be conducted to confirm this interaction.

Herbal substances have the potential to modify the pharmacokinetics of co-administered pharmaceuticals, resulting in changes in drug concentrations in the body (45). APE has been shown to decrease the  $C_{max}$  value in most bronchodilators and anti-inflammatory medicines, indicating that the concentration of pharmaceuticals entering the systemic circulation has decreased. Over this period, the highest concentration of the medication in the blood had no measurable impact on  $T_{max}$  variations; the drug's onset was not clinically meaningful.

Previous studies found that APE and AND, respectively, have antidiabetic activities by lowering blood glucose levels in GLUT-4 diabetic mice; such activities are indicated by the increased mRNA expression and protein synthesis, resulting in the increased translocation of GLUT-4 to the plasma membrane (57,58). AND has been shown to lower blood glucose, LDL, and triglycerides in diabetic rats fed with a high-fructose diet (59). In streptozotocin-induced diabetic rats, the mechanism of action of AND possibly involves an increase in the expression levels of pancreatic beta cells and insulin (60). Furthermore, AND can reduce acetylcholinergic activity, oxidative stress, hyperglycemia, and insulin deficiency in patients with diabetes mellitus (61).

With this potential antidiabetic activity, many herbal medicinal preparations derived from *A. paniculata* are used by patients with diabetes mellitus. Potential HDIs in combination with some oral antidiabetic drugs, such as glyburide, glimepiride, and metformin, elicit synergistic effects that increase antidiabetic activities (34,35). As it was said APE and AND can inhibit or induce the performance of sulfonylurea drug-metabolizing enzymes, such as CYP3A4, CYP2C9, and CYP2C19. This ability predicts the interaction mechanism in terms of pharmacokinetics with oral antidiabetic drugs (62–64). A significant increase in  $C_{max}$  and AUC of glyburide and glimepiride in combination with AND suggests that CYP3A4 may be inhibited; as a result, the blood levels of the intact drug increase because of the decreased metabolic activity (34,35). Likewise, APE can inhibit gliclazide metabolism by inhibiting CYP2C9 and CYP3A4 activities, thereby decreasing the levels of this drug in the blood and changing the pharmacokinetic parameters (33). The difference in the mechanism of HDIs with tolbutamide is characterized by a decrease

in  $C_{max}$  and AUC because APE and AND act on other metabolizing enzyme pathways, specifically by increasing the expression of CYP2C6/11 protein; consequently, tolbutamide blood levels decrease (32). Furthermore, warfarin and midazolam likely have HDIs that involve the inhibition of CYP2C9 and CYP3A4 enzymes by AND. This mechanism then causes a decrease in the metabolism of both drugs, resulting in significantly higher intact drug levels in the blood (36,37). Conversely, drugs that have HDIs with metformin are not metabolically active. Therefore, changes in pharmacokinetic parameters are strongly suspected because of the mechanism of inhibition or induction of metformin transporter OCTs (OCT1, OCT2, and OCT3) and MATEs (65).

HDIs mechanism in pharmacokinetics does not necessarily correlate with changes in pharmacological effects. HDIs have different pharmacokinetic and pharmacodynamic pathways. According to their affinity for the common site of action, herbal medications may have synergistic or additive effects with the conventional drug (2,66). However, the phytovigilance for potential HDIs becomes complicated because of an herb's multiple constituents, confusion caused by the use of shared common plant names, misidentification of species, mislabeling of products, contamination, the extraction process, and herb combination or use of multiherbal products. In comparison with extracts, the full complement of constituents in whole plant parts may affect the pharmacodynamics and pharmacokinetics of “the full complement” in cannabis research.

## Conclusion

This review on pharmacokinetic and pharmacodynamic aspects reveals that APE and AND have potential HDIs with several drugs. APE and AND, as substrates of the CYP450 enzyme family, cause changes in intact drug levels in the blood, likely changing the pharmacokinetic parameters of drugs. Pharmacological activity suggests that APE and AND may elicit a synergistic effect when they are combined with anti-inflammatory and antidiabetic drugs. This study serves as a framework for clinical therapy considerations in HDIs. However, further investigations involving clinical trials that are more supportive of clinical applications should be performed.

## Author's contributions

ES prepared the manuscript, EL, AN, and AEN edited the manuscript. All authors reviewed, confirmed, and approved the final version of the manuscript.

## Conflict of interests

The authors declare no conflict of interest.

## Ethical considerations

In order to avoid plagiarism, misconduct, data fabrication, falsification, duplicate publishing or submission, and

redundancy, the authors have taken a great effort to monitor and document these ethical concerns.

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