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Review Article

Pharmacokinetic and Pharmacodynamics Interactions between *Andrographis paniculata*, Andrographolide, and Oral Antidiabetic Drugs: A Systematic Review of Preclinical Evidence

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ABSTRACT

Herb–drug interactions between *Andrographis paniculata*, its constituent andrographolide, and oral antidiabetic drugs may alter drug exposure and glycemic responses. In this systematic review, we assessed the pharmacokinetic and pharmacodynamics interactions between *A. paniculata* or andrographolide and oral antidiabetic drugs. We searched PubMed, Scopus, ScienceDirect, SpringerLink, Web of Science, EBSCOhost, Portal Garuda, and other databases for articles published through August 2025. Search terms included free-text and Medical Subject Headings (MeSH) keywords: "Herb–Drug Interactions," andrographolide, *Andrographis paniculata*, and oral antidiabetic drugs (MeSH: Hypoglycemic Agents). Sixty-one records were identified; 10 preclinical reports were included, and no eligible human clinical studies were found. Heterogeneity in preparation type, dosing, and study design precluded meta-analysis; therefore, a narrative synthesis was performed. Across the included studies, combinations of *A. paniculata* or andrographolide with sulfonylureas often significantly increased drug exposure (maximum plasma concentration [C_{max}]; area under the concentration–time curve [AUC]) and enhanced glucose-lowering. Repeated andrographolide dosing significantly reduced glipizide exposure and attenuated its effects. Tolbutamide exhibited pharmacokinetic–pharmacodynamics dissociation, with significantly reduced exposure but preserved hypoglycemic activity. Saxagliptin exposure increased with reduced clearance; repaglinide showed higher C_{max} and AUC with augmented glucose-lowering effects; metformin exhibited increased exposure with enhanced glycemic control; and acarbose showed no meaningful change. Overall, the findings suggest that *A. paniculata* and andrographolide potentiate the pharmacokinetic/pharmacodynamics effects of some oral antidiabetic drugs, whereas acarbose shows no interaction. Glipizide exhibits either synergistic or antagonistic effects depending on the preparation type. These context-dependent findings highlight the need for preparation-specific evaluation and clinical verification.

Keywords: *Andrographis paniculata*, Andrographolide, Herb–Drug Interactions, Pharmacokinetics, Pharmacodynamics, Oral Antidiabetic Drugs.

Introduction

Diabetes mellitus (DM) has become one of the most significant global health challenges. Approximately 830 million people were living with diabetes in 2022 (14% of adults aged ≥ 18 years; > 95% with type 2), underscoring continued burden of DM on health systems.[1] Concurrently, the use of herbal medicines for chronic diseases is widespread, with substantial global uptake.[2–4] Among patients with diabetes, this pattern is mirrored: in Africa, 12.4%–77.1% of individuals with diabetes report using traditional medicine, with 35.4%–88.4% taking it concurrently with conventional drugs.[5] Another study reported that approximately 72.8% of patients use herbal medicines or supplements concurrently with conventional therapy.[6] Similar findings have been reported elsewhere, with concomitant herbal use reaching 68% in Saudi Arabia and 54.3% in Ethiopia.[7,8]

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Collectively, these data suggest that adjunctive herbal use among people with diabetes is common across populations. Notably, many patients (63.8%–91.3%) do not disclose their herbal medicine use to healthcare professionals,[5,7] allowing potential herb–drug interactions (HDIs) to go undetected.[9,10] HDIs may be pharmacokinetic (PK) or pharmacodynamics (PD), with clinical consequences ranging from therapeutic failure to dangerous hypoglycemia.[6,11] In routine practice, HDI risks are often overlooked owing to suboptimal pharmacovigilance, limited clinical guidance, inadequate documentation of herbal products consumed, and patient reluctance to report use.[5,12]

In Asia (including Indonesia), *Andrographis paniculata* (AP) is commonly used, and its principal constituent, andrographolide (AN), has been extensively investigated in preclinical models for antidiabetic and anti-inflammatory effects.[13,14] *In vitro* evidence indicates that AP extracts and AN modulate several cytochrome P450 (CYP) isoenzymes.[15] Specifically, AP extract inhibits CYP3A4 and CYP2C9, whereas AN downregulates CYP3A expression and activity in hepatocytes.[16,17] These findings are clinically relevant because many oral antidiabetic drugs (OADs), such as sulfonylureas (including glibenclamide, glipizide), are metabolized primarily by CYP2C9, with contributions from CYP3A4,[18,19] suggesting that AP-mediated enzymatic inhibition could increase drug exposure and heighten hypoglycemia risk.[15] Conversely, metformin undergoes negligible CYP metabolism; its interactions are mediated by organic cation transporters

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(e.g., OCT1/2/3) and multidrug and toxin extrusion transporters (including MATE1/2-K), which govern drug uptake and excretion.[20,21]

Given the substantial burden of type 2 DM and widespread unsupervised herbal use, the risks of HDIs between AP/AN and OADs warrant systematic evaluation. Evidence gaps regarding enzyme-mediated versus transporter-mediated mechanisms and the translational relevance of preclinical findings motivated this review. In this systematic review, we aimed to appraise and synthesize preclinical *in vivo* evidence on PK and PD interactions between AP/AN and OADs, characterize changes in key PK parameters (e.g., maximum plasma concentration [C_{max}], area under the concentration–time curve [AUC], and clearance) and glucose-lowering responses, elucidate underlying CYP- and OCT/MATE-mediated mechanisms, and assess clinical implications and research gaps to support safer practice.

Materials and Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines.[22]

Materials

Reference management was performed using Zotero (version 6.0.26, Zotero Foundation) to organize the identified records and manage citations.

Methods

Information sources and search strategy

We searched PubMed, Scopus, Web of Science (Core Collection), EBSCOhost, ScienceDirect, SpringerLink, and Portal Garuda for articles published through August 2025. Furthermore, we conducted backward citation tracking (the included studies' reference lists) and targeted web searches, which yielded two additional records. For the search strategies, we combined free-text and indexed terms for AP, sambiloto, AN, andrografolida, OADs, HDIs, PK, and PD, with Boolean operators tailored to each platform. For PubMed, Medical Subject Headings (MeSH) were also applied, combining "Herb–Drug Interactions" [MeSH] AND (pharmacokinetics OR pharmacodynamics) AND *Andrographis paniculata* (Burm. f.) AND andrographolide. Records were managed in Rayyan[23] for centralized deduplication and title/abstract screening. Duplicates were removed before screening, and the selection process is illustrated in the PRISMA flow diagram (Figure 1).

Data extraction

Data were extracted using a piloted, standardized form capturing: author and year, study type/design and animal model, OAD type, AP/AN preparation (extract or pure compound), dosing regimen (dose, route, and treatment duration), PK endpoints (including AUC, time to maximum concentration, half-life, apparent clearance after oral administration [CL/F], and volume of distribution), PD outcomes (such as change in blood glucose, glucose AUC, and hypoglycemia), and mechanistic notes when available (including for CYP2C9/CYP3A4, OCT/MATE).

Eligibility criteria

Inclusion was limited to *in vivo* animal (preclinical) and human clinical studies conducted to evaluate the PK and/or PD interactions between

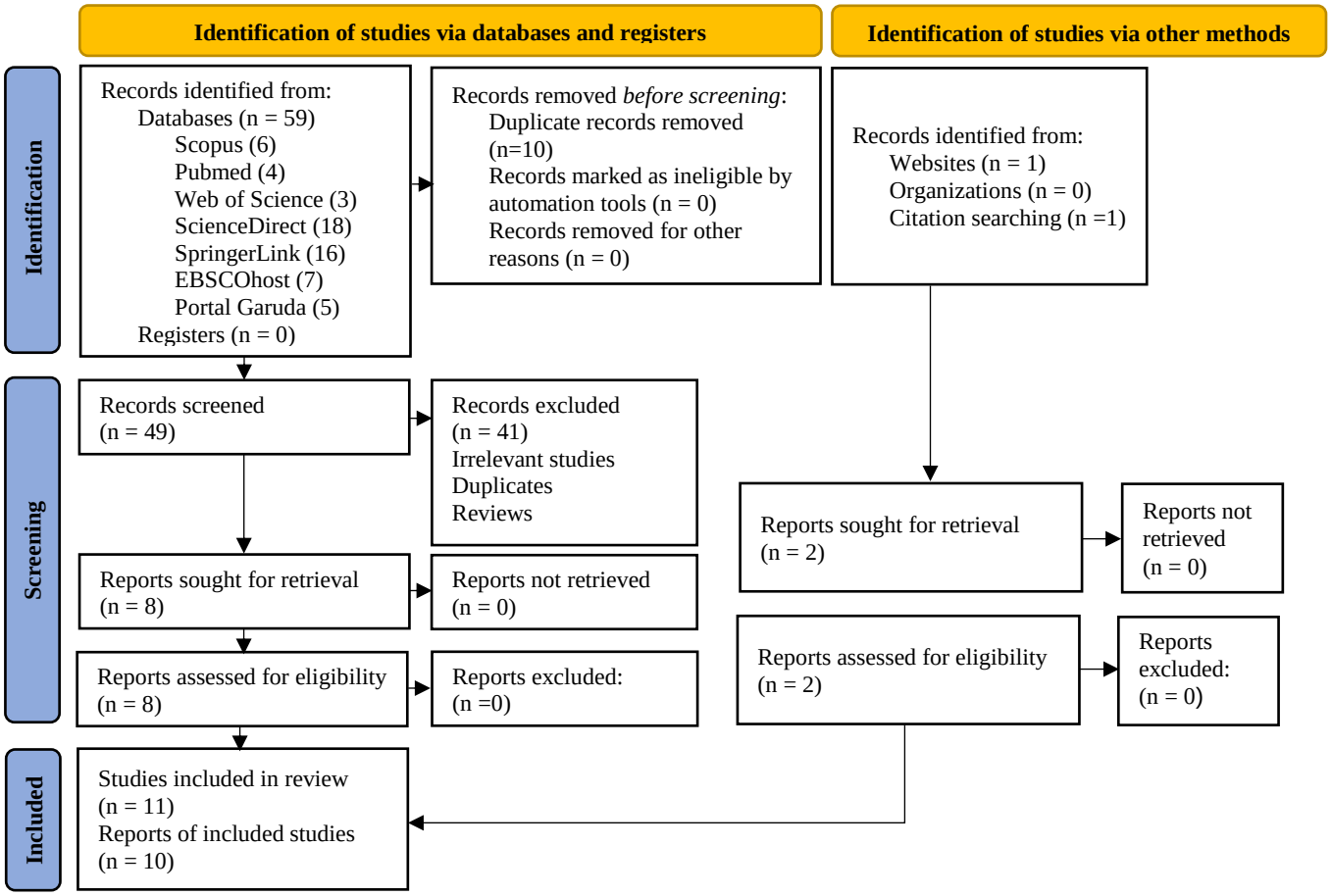

Figure 1: Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram of study selection. Adapted from PRISMA 2020[22]. One report[26] includes two studies analyzed separately (*Andrographis paniculata* + glimepiride; andrographrolide + metformin); therefore, the number of studies (n = 11) exceeds the number of reports (n = 10)

AP/AN and OADs. Original articles published in English or Indonesian were considered. Reviews, conference proceedings, letters, editorials, case reports, theses, and non-*in vivo* studies were excluded.

Risk of bias assessment
The risk of bias in the included animal studies was assessed using the SYRCLE RoB tool (10 domains).[24]

Synthesis methods
Given the heterogeneity in study designs and outcomes, we performed a structured narrative synthesis following the Synthesis Without Meta-analysis (SWiM) guidance,[25] organized thematically. Results are presented in layers: (i) study characteristics, (ii) risk-of-bias assessment, (iii) individual study findings, and (iv) cross-study thematic synthesis.

Results and Discussion

Study selection
We identified 59 records from databases through the search and two additional records from other sources (one from a website, one from a backward citation), totaling 61. After removing 10 duplicates, 51 records were screened by title/abstract, and 41 were excluded. The most common reasons for exclusion at the title/abstract stage were lack of relevance to PK/PD interactions between AP/AN and OADs (such as not evaluating co-administration), article type (reviews or reports), and multi-herb regimens (that is, co-administration involving more than one herbal medicine). Ten full-text reports were assessed for eligibility, and none were excluded (full-text exclusions: 0; all assessed reports were eligible). No human clinical trials were identified; all included studies were preclinical animal studies. Human clinical studies were prespecified in the review protocol, but none met the eligibility criteria. One report[26] contained two independent studies, yielding 11 studies across 10 reports, consistent with the PRISMA 2020 distinction between reports and studies[22] **(**Figure 1).

Study characteristics
Rat models were used in all included studies under both normoglycemic and diabetic conditions, with the latter being induced using streptozotocin (STZ), nicotinamide plus STZ (NA+STZ), alloxan, a high-fat, high-fructose diet, or a high-fat diet combined with NA and STZ (HFD+NA+STZ). Herbal interventions consisted of AP preparations (infusion, extract, or pure AN) administered alongside OADs. Drug concentrations were typically quantified using validated high-performance liquid chromatography; liquid chromatography–tandem mass spectrometry was employed in one study (saxagliptin). Detailed study characteristics and per-study outcomes are summarized in Table 1.[26–35]

Risk of bias in studies
The risk of bias in animal studies was assessed using the SYRCLE Risk of Bias tool, comprising 10 domains: selection (sequence generation, baseline characteristics, allocation concealment), performance (random housing, blinding of caregivers/investigators), detection (random outcome assessment, blinding of outcome assessor), attrition (incomplete outcome data), reporting (selective reporting), and other biases.[24] Study-level judgements are summarized in Table 2. The distribution of risk-of-bias ratings by domain is visualized in Figure 2 (bar plot), showing proportions of low, unclear, and high risk. Generally, random housing and blinding of caregivers/investigators were often unclear, whereas incomplete outcome data and selective reporting were consistently low across all studies.

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Individual study findings
The PK/PD outcomes of the individual studies are summarized in Table 1**.** Unless otherwise specified, most regimens were short-term (typically 5–7 days). Among sulfonylureas, regimens in which AP or AN was administered as a pretreatment before a sulfonylurea dose generally showed significant increases in exposure (C_{max} and/or AUC), accompanied by strengthened glucose-lowering responses for glyburide/glibenclamide, glimepiride, and gliclazide, with notable exceptions for tolbutamide and specific glipizide–AN regimens. Tolbutamide showed significantly decreased exposure (AUC), whereas the acute hypoglycemic effect remained largely unchanged. In 28-day co-administration regimens in diabetic rats, glipizide showed more divergent patterns: co-administration with AP extract resulted in significant increases in exposure and improved glucose-lowering compared with using glipizide alone, whereas co-administration with AN produced a pronounced, significant decrease in exposure accompanied by a weaker, shorter glucose-lowering response (Table 1). In studies using AP herb infusion, 7-day co-administration of glibenclamide with a higher AP dose (500 mg/kg) yielded a greater reduction in blood glucose than did glibenclamide alone, although PK parameters were not reported.

For saxagliptin, pretreatment with AN resulted in significantly increased C_{max} and AUC and significantly reduced CL/F in a dose-dependent manner (30 versus 100 mg/kg), consistent with an enhanced hypoglycemic effect. Repaglinide also exhibited significant increases in exposure and potentiated glucose-lowering following AN pretreatment, particularly after multiple-day regimens. Metformin showed significant increases in exposure and augmented the PD effects post-AN pretreatment. In contrast, in insulin-resistant rats, co-administration of metformin with purified AP extract was associated with a reduced glucose-lowering effect, without PK data (Table 1). Finally, the acarbose–AP extract combination exhibited a null-interaction profile, with no significant alteration in its hypoglycemic effect

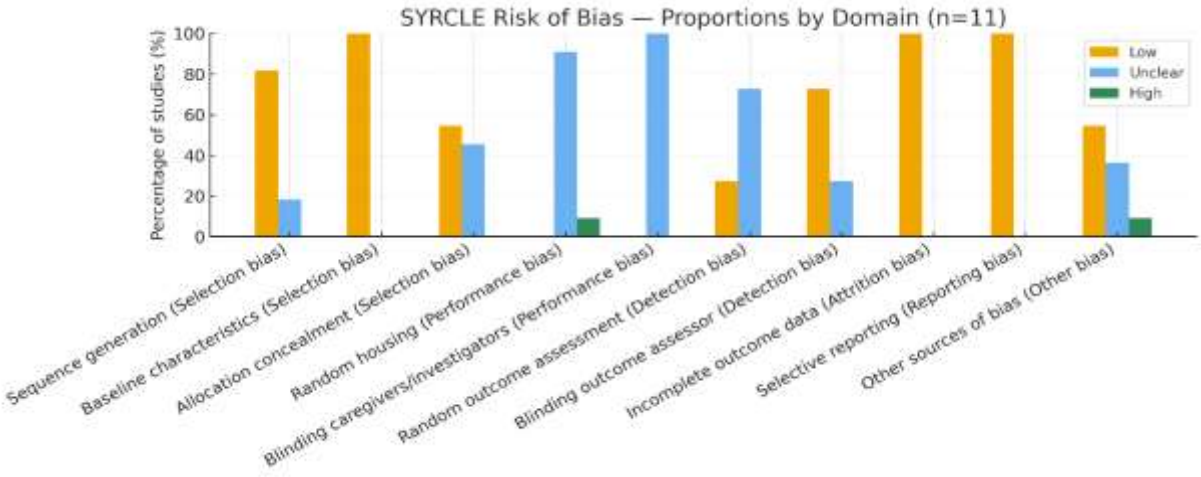

Figure 2: Proportions of SYRCLE risk-of-bias ratings by domain (n = 11; low, unclear, high; bars show percentage of studies)

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Table 1: Characteristics and outcomes of preclinical studies investigating pharmacokinetic and pharmacodynamics interactions between *Andrographis paniculata* (AP) or andrographolide (AN) and oral antidiabetic drugs

Drugs	Intervention (AP/AN)	Drug dose	Intervention dose	Administration	Model & sample (n)	Study design	PK profile		PD outcome	References
							Increased	Decreased		
Glimepiride	AN	1 mg/kg bw	4.5 mg/kg bw	Oral	Male Wistar rats, normal (n = 6 per group)	Parallel-group; 7-day pretreatment + glimepiride (day 8)	C_{max} 1.96×**, AUC_{0}–t 2.95×**, AUC_{0}–∞ 3.24×**, t½ 2.06×**, MRT 1.53×**	CL 0.32×**, Vd 0.63×**, T_{max} ↔	Greater glucose-lowering versus glimepiride alone.	26
Glimepiride	AN	1 mg/kg bw	4.5 mg/kg bw	Oral	Male Wistar rats, diabetic (n = 6 per group)	Parallel-group; 7-day pretreatment + glimepiride (day 8)	C_{max} 2.95×**, AUC_{0}–t 2.89×**, AUC_{0}–∞ 2.95×**, t½ 1.29×**, MRT 1.18×**	CL 0.34×**, Vd 0.5×**, T_{max} ↔	Greater glucose-lowering versus glimepiride alone.	
Tolbutamide	AP extract	20 mg/kg bw	2 g/kg bw	Oral	PK: Male Sprague–Dawley rats, normal (n = 5 per group) PD: C57BL/6 mice, HFD-induced obese, hyperglycemic (n = 6)	Parallel-group; 5-day pretreatment + tolbutamide (day 6)	n.d.	$AUC_{0–12h}$ 37%*, T_{max}, MRT*, C_{max}	No change in glucose-lowering with tolbutamide; fasting glucose and glucose AUC were lower.	
Tolbutamide	AN	20 mg/kg bw	50 mg/kg bw	Oral	Male Sprague–Dawley rats, normal (n = 5 per group) PD: C57BL/6 mice, HFD-induced obese, hyperglycemic (n = 8)	Parallel-group; 5-day pretreatment + tolbutamide (day 6)	C_{max}, MRT	$AUC_{0–12h}$ 18%*, T_{max} ↔	No change in glucose-lowering with tolbutamide; fasting glucose and glucose AUC were lower.	27
Glyburide	AN	10 mg/kg bw	4.5 mg/kg bw	Oral	Male Wistar rats, normal (n = 6 per group)	Parallel-group; 7-day pretreatment + glyburide (day 8)	C_{max} 1.6×*, AUC_{0}–t 1.48×*, AUC_{0}–∞ 1.49×*, t½ 1.1×, MRT 1.1×	CL 0.77×*, Vd 0.64×*, T_{max} ↔	Greater glucose-lowering versus glyburide alone.	
Glyburide	AN	10 mg/kg bw	4.5 mg/kg bw	Oral	Male Wistar rats, diabetic (n = 6 per group)	Parallel- group; 7-day pretreatment + glyburide (day 8)	C_{max} 1.66×*, AUC_{0}–t 1.65×*, AUC_{0}–∞ 1.65×*, t½ 1.06×, MRT 1.07×*	CL 0.60×*, Vd 0.62×*, T_{max} ↔	Greater glucose-lowering versus glyburide alone.	28
Glibenclamide	AP infusion	0.9 mg/200 g bw	250 mg/kg bw	Oral	Male Sprague–Dawley rats (n = 4 per group)	Parallel-group; co-administration for 7 days	n.d.	n.d.	No clear change in glucose-lowering versus glibenclamide alone.	
Glibenclamide	AP infusion	0.9 mg/200 g bw	500 mg/kg bw	Oral	Male Sprague–Dawley rats (n = 4 per group)	Parallel-group; co-administration for 7 days	n.d.	n.d.	Greater glucose-lowering versus glibenclamide alone.	29
Gliclazide	AP extract	2 mg/kg bw	2 g/kg bw	Oral	Male and female Wistar rats,	Parallel-group; 7-day pretreatment + gliclazide (day 8)	C_{max}*, T_{max}, t½*, AUC_{0}–∞**, $AUMC_{0}$-∞**, MRT_{0}-∞	Vd**, CL	n.d.	30

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					normal (n = 6 per group)					
Glipizide	AP extract	5 mg/kg bw	300 mg/kg bw	Oral	Male Wistar rats, normal (n = 5 per group)	Parallel-group; 7-day pretreatment + glipizide (day 7)	C_{max} 1.05×, AUC_0–t 1.12×, Vd/F 1.09×	AUC_0–∞ 0.93×, $AUMC_0$–∞ 0.59×, t½ 0.6×, CL/F 0.64×, MRT_0–∞ 0.62×	n.d.	
Glipizide	AN	5 mg/kg bw	15 mg/kg bw	Oral	Male Wistar rats, normal (n = 5 per group)	Parallel-group; 7-day pretreatment + glipizide (day 7)	C_{max} 1.25×, T_{max} 1.07×, AUC_0–t 1.43×, AUC_0–∞ 1.2×	$AUMC_0$–∞ 0.82×, t½ 0.58×, Vd/F 0.86×, CL/F 0.46×, MRT_0–∞ 0.64×	n.d.	
Glipizide	AP extract	5 mg/kg bw	300 mg/kg bw	Oral	Male Wistar rats, diabetic (n = 5 per group)	Parallel-group; co-administration for 28 days	C_{max} 2.62×**, AUC_0–t 1.75×**, Vd/F 1.01×	AUC_0–∞ 0.75×, $AUMC_0$–∞ 0.24×, t½ 0.35×, CL/F 0.41×, MRT_0–∞ 0.68×	Greater glucose-lowering versus glipizide alone.	[31]
Glipizide	AN	5 mg/kg bw	15 mg/kg bw	Oral	Male Wistar rats, diabetic (n = 5 per group)	Parallel-group; co-administration for 28 days	C_{max} 0.11×**, T_{max} 1.23× CL/F 7.4×**, Vd/F 12.5×**	AUC_0–t 0.10×**, AUC_0–∞ 0.073×**, $AUMC_0$–∞ 0.05×, t½ 0.6×, MRT_0–∞ 0.62×	Weaker and shorter glucose-lowering than glipizide alone, consistent with reduced bioavailability.	
Metformin	AN	100 mg/kg bw	4.5 mg/kg bw	Oral	Male Wistar rats, normal (n = 6 per group)	Parallel-group; 7-day pretreatment + metformin (day 8)	C_{max} 1.65×**, AUC_0–t 2.13×**, AUC_0–∞ 2.24×**, t½ 1.26×**, MRT 1.22×**	CL 0.45×**, Vd 0.57×**, T_{max} ↔	Greater glucose-lowering versus metformin alone.	
Metformin	AN	100 mg/kg bw	4.5 mg/kg bw	Oral	Male Wistar rats, diabetic (n = 6 per group)	Parallel-group; 7-day pretreatment + metformin (day 8)	C_{max} 3.17×**, AUC_0–t 5.11×**, AUC_0–∞ 7.16×**, t½ 2.18×**, MRT 2.0×**	CL 0.58×**, Vd 0.31×**, T_{max} ↔	Greater glucose-lowering versus metformin alone.	[26]
Metformin	Purified AP extract	22.5 mg kg bw	434.6 mg/kg bw	Oral	Male Sprague–Dawley rats n = 6 per group)	Parallel-group; co-administration, b.i.d., 5 days	n.d.	n.d., authors suggested reduced absorption → lower bioavailability	Reduced glucose-lowering versus metformin alone.	
Metformin	Purified AP extract	45 mg/kg bw	434.6 mg/kg bw	Oral	Male Sprague–Dawley rats n = 6 per group)	Parallel-group; co-administration, b.i.d., 5 days	n.d.	n.d., authors suggested reduced absorption → lower bioavailability	Reduced glucose-lowering versus metformin alone.	[32]
Repaglinide	AN	1 mg/kg bw	4.5 mg/kg bw	Oral	Male Wistar rats, diabetic (n = 6 per group)	Parallel-group; AN single-dose followed by repaglinide (SDT; same day)	C_{max} 1.12×*, AUC_0–t 1.33×*, $AUMC_0$–t 1.07×**, t½ 1.36×, MRT 1.37×*	CL 0.86×*, Vd 0.85×**, Vdss 0.76×**, T_{max} ↔	Greater glucose-lowering versus repaglinide alone.	[33]
Repaglinide	AN	1 mg/kg bw	4.5 mg/kg bw	Oral	Male Wistar rats, diabetic (n = 6 per group)	Parallel-group; 7-day pretreatment + repaglinide (MDT; day 8)	C_{max} 1.77×**, AUC_0–t 1.76×**, $AUMC_0$–t	CL 0.35×**, Vd 0.78×**, Vdss 0.61×**, T_{max} ↔	Greater and more consistent glucose-	

							1.2×**, t½ 2.15×**, MRT 1.77×**		lowering than SDT.	
Saxagliptin	AN	10 mg/kg bw	30 mg/kg bw	Oral	Male Sprague–Dawley rats, diabetic (n = 6 per group)	Parallel-group; 7-day pretreatment + saxagliptin (day 8)	C_{max}*, $AUC_{0–t}$*, AUC0–∞, $t½$*, MRT*	CLz/F**, T_{max} ↔	Increased glucose-lowering to near-normal at 24 h	
Saxagliptin	AN	10 mg/kg bw	100 mg/kg bw	Oral	Male Sprague–Dawley rats, diabetic (n = 6 per group)	Parallel-group; 7-day pretreatment + saxagliptin (day 8)	C_{max}*, $AUC_{0–t}$*, $AUC_{0–\infty}$, $t½$*, MRT*, (greater than 30 mg/kg)	CLz/F* (lower than 30 mg/kg), T_{max} ↔	Faster normalization (~12 h); hypoglycemia observed during the time course.	34
Acarbose	AP extract	2.05 mg/kg bw	234 mg/kg bw	Oral	Wistar rats, diabetic (n = 3 per group)	Parallel-group; co-administration for 7 days	n.d.	n.d.	No clear change in glucose-lowering versus acarbose alone.	35

Notes. n.d., not determined/not reported; AP, *Andrographis paniculata*; AN, andrographolide; OAD, oral antidiabetic drug(s); bw, body weight; AUC, area under the plasma concentration–time curve; AUMC, area under the first-moment curve; subscripts 0–t and 0–∞ denote integration from time 0 to the last quantifiable time point and to infinity, respectively; C_{max}, maximum (observed) plasma concentration; T_{max}, time to reach $C_{max;}$ t½, elimination half-life (time for plasma concentration to decline by 50%); MRT, mean residence time; CL, clearance; CL/F, apparent oral clearance; CLz/F, terminal-phase apparent oral clearance; Vd, apparent volume of distribution; Vd/F, apparent volume of distribution after oral dosing; Vdss, volume of distribution at steady state; SDT, single-dose treatment; MDT, multiple-dose treatment; h, hour(s); ~, approximately. Symbols: ↑, increased; ↓, decreased; ↔, no statistically significant difference; ×, fold (multiplicative change), +, followed by drug. Significance: * and ** indicate statistically significant differences compared to monotherapy ($p < 0.05$; $p < 0.01$; two-sided tests), as reported in each study.

Synthesis of pharmacokinetic–pharmacodynamics interaction patterns

Heterogeneity in preparation type, dose, treatment duration, and disease model (Table 1), as well as variable methodological quality (Table 2, Figure 2), made meta-analysis infeasible. Therefore, a thematic narrative synthesis was conducted in line with PRISMA/SWiM guidance,[25] focusing on three PK–PD interaction patterns: synergy, antagonism, and PK–PD dissociation (that is, induction-mediated PK decrease with preserved PD). Individual-study results are summarized as combination-to-monotherapy contrasts for C_{max} and AUC, alongside the direction of PD change (↑/↓) to facilitate interpretation. Using this common framework, three recurring PK–PD patterns—synergistic, antagonistic, and dissociation—emerged across the included studies, each linked to specific metabolic or transporter pathways.

A predominantly synergistic pattern was observed across most AP/AN–OAD combinations. In regimens involving pretreatment with AP extract or AN followed by combined AP/AN–OAD dosing, sulfonylurea-based therapies (glibenclamide/glyburide, glimepiride, gliclazide, and glipizide), repaglinide, saxagliptin, and metformin generally showed higher OAD exposure and stronger glucose-lowering effects than did monotherapy. A comparable synergistic pattern was also observed with the continuous co-administration of glipizide and AP extract without a distinct pretreatment phase.

Collectively, these regimens typically produced significant increases in OAD C_{max}, AUC, or both, accompanied by more pronounced or sustained antihyperglycemic responses compared with those with OAD alone (Table 1). Consistent with this overall pattern, co-administration of glibenclamide with a higher-dose AP herb infusion produced greater glucose-lowering than did glibenclamide alone, despite the absence of PK measurements in that study, thereby reinforcing a predominantly synergistic profile at the PD level. Only a small subset of AP/AN–OAD regimens deviated from this dominant synergistic profile. Repeated AN (15 mg/kg) co-administered with glipizide (5 mg/kg) in diabetic rats produced marked decreases in C_{max} and $AUC_{0–t}$ to approximately 0.11-fold and 0.10-fold of the monotherapy values, respectively, along with a weaker and shorter hypoglycemic response, consistent with an antagonistic induction-mediated interaction. For tolbutamide, co-administration with AP extract or AN reduced the AUC by 37% and 18%, respectively, without attenuating the acute hypoglycemic effect (Table 1), indicating PK–PD dissociation. In insulin-resistant rats, metformin combined with purified AP extract produced a lower glucose-lowering effect than did metformin alone, in the absence of PK measurements, suggesting possible PD antagonism rather than a confirmed PK–PD interaction (Table 1). In contrast, acarbose co-administered with AP extract did not materially alter glycemic outcomes, consistent with a null-interaction profile that aligns with its predominantly local intestinal mechanism of action.

Moderators of interaction

As shown in Table 1, the direction and magnitude of PK–PD interaction were shaped by three main factors: (i) preparation type (infusion, ethanolic extract, or pure compound), dose, and treatment duration; (ii) disease status (normoglycemic versus diabetic), given diabetes-associated shifts in enzyme/transporter expression and organ perfusion; and (iii) the principal biotransformation and transport pathways implicated (CYP2C9, CYP3A4, CYP2C8, uridine 5'-diphospho-glucuronosyltransferase [UGT], OATP1B1, P-gp, plasma membrane monoamine transporter [PMAT]/OCT1, OCT2/MATE). Collectively, these factors can tilt the mechanistic balance toward either inhibition- or induction-predominant net effects. This heterogeneity, combined with the variable risk of bias across studies (Table 2, Figure 2), precluded quantitative synthesis and justified a narrative approach in line with PRISMA 2020 and SWiM guidance.[22]

Mechanistic interpretation of pharmacokinetic–pharmacodynamics patterns

The observed PK–PD profiles are interpreted in relation to AP- or AN preparation-mediated modulation of drug-metabolizing enzymes, transporters, and local intestinal actions. Each interaction pattern (synergistic, antagonistic, or showing PK–PD dissociation) is linked to plausible mechanistic drivers, including enzyme inhibition or induction, transporter modulation, and predominantly local intestinal effects. Collectively, these mechanisms span a continuum from predominantly enzyme-mediated clearance to transporter-dependent elimination and locally active intestinal pathways.

Mechanistic insights: enzyme-mediated interactions (sulfonylureas)

Most second-generation sulfonylureas are cleared primarily through CYP2C9, with minor contributions from CYP3A4 and, for some agents, such as glipizide, CYP2C19.[30,36] This class-level disposition aligns with the predominantly synergistic pattern observed with AP/AN co-administration: AP extract- or AN-mediated inhibitory modulation of CYP2C9 (and, to a lesser extent, CYP3A4/CYP2C19) would be expected to increase systemic exposure and, in turn, potentiate glucose-lowering efficacy across agents such as glibenclamide

Table 2: Risk-of-bias assessment of the included animal studies based on the SYRCLE tool across ten domains

Study	1 Sequence generation (Selection bias)	2 Baseline characteristics (Selection bias)	3 Allocation concealment (Selection bias)	4 Random housing (Performance bias)	5 Blinding of caregivers/investigators (Performance bias)	6 Random outcome assessment (Detection bias)	7 Blinding of outcome assessor (Detection bias)	8 Incomplete outcome data (Attrition bias)	9 Selective reporting (Reporting bias)	10 Other sources of bias (Other bias)
Samala and Veeresham [26]	√	√	√	?	?	?	√	√	√	√
Samala and Veeresham [26]	√	√	√	?	?	?	√	√	√	√
Chen *et al*.[27]	√	√	?	?	?	?	?	√	√	√
Samala and Veeresham [28]	√	√	?	?	?	?	?	√	√	?
Sari *et al*.[29]	?	√	?	?	?	?	?	√	√	?
Mouid[30]	√	√	√	?	?	?	√	√	√	√
Sundhani *et al*.[31]	√	√	√	?	?	√	√	√	√	√
Syamsul *et al*.[32]	√	√	?	?	?	?	√	√	√	?
Nandru *et al*.[33]	√	√	√	?	?	√	√	√	√	√
Wu *et al*.[34]	√	√	√	?	?	√	√	√	√	√
Sukmawati *et al*.[35]	?	√	?	×	?	?	√	√	√	×

Note. The two rows for Samala and Veeresham[26] correspond to studies distinct from this report: andrographolide (AN) + glimepiride and AN + metformin, respectively. Both studies were derived from a single report; therefore, RoB judgements were identical. Symbols: √ = low risk, × = high risk, ? = unclear risk

glyburide, glimepiride, gliclazide, and glipizide. This interpretation is also consistent with pharmacogenetic evidence linking reduced CYP2C9 activity to higher sulfonylurea concentrations and greater hypoglycemia risk, [37,38] and with preclinical data showing inhibition of CYP2C9 and CYP3A4, with possible CYP2C19 involvement, by AP preparations and AN.[26,28,30,31,33,34]

In contrast, repeated co-administration of AN and glipizide in diabetic rats yielded an antagonistic PK–PD pattern. Induction of CYP2C9 (with minor CYP3A4 involvement) and associated clearance pathways (UGT, P-gp) most likely explain the marked reduction in exposure and the shorter, weaker hypoglycemic responses.[31] Tolbutamide was an exception, exhibiting PK–PD dissociation: exposure decreased under AP/AN co-administration, yet the acute hypoglycemic effect was largely preserved. This pattern is consistent with the induction of hepatic CYP1A/2C/3A, UGT, and P-gp, which increase metabolic/efflux capacity while maintaining PD sensitivity.[16,27] Overall, these findings indicate that while most sulfonylureas exhibit a synergistic PK–PD relationship under AP/AN co-administration, glipizide under prolonged AN exposure tends toward antagonism, whereas tolbutamide shows PK–PD dissociation, warranting compound-specific monitoring of glycemic control. Unlike sulfonylureas, which are primarily cleared by CYP2C9, certain agents exemplify a more selective form of enzyme modulation, being predominantly metabolized by CYP3A4/5 to an active metabolite.

Mechanistic insights: enzyme-mediated modulation (saxagliptin)

The reported pharmacokinetic increase in saxagliptin exposure following AN pretreatment[34] is consistent with CYP3A4-mediated inhibition of metabolic clearance and corresponds to a synergistic PK–PD interaction pattern. This mechanistic interpretation reflects the established disposition of saxagliptin, which undergoes extensive CYP3A4/5-mediated oxidation to its active metabolite, 5-hydroxysaxagliptin, and exhibits marked sensitivity to both potent CYP3A4 inhibitors and inducers.[39–41] This explanation is consistent with findings from *in vitro* studies in which AP and AN are classified as mild-to-moderate CYP3A4 inhibitors.[42] Comparable effects are observed with moderate CYP3A4 inhibitors such as grapefruit juice, which similarly increase saxagliptin exposure.[43] The concordance between PK enhancement and PD potentiation indicates a synergistic mechanism where metabolic inhibition amplifies glucose-lowering efficacy. Collectively, these preclinical findings indicate that clinically relevant HDIs are plausible, and that AP or AN co-administration may alter saxagliptin plasma levels. This finding warrants careful glucose monitoring and further clinical evaluation. Beyond these enzyme-mediated mechanisms, several OADs also modulate enzymatic and transporter pathways, reflecting a more intricate PK interplay.

Mechanistic insights: transporter- and enzyme-driven interactions (repaglinide)

The reported PK increase in repaglinide exposure following AN pretreatment[33] is most likely owing to inhibition of CYP3A4-mediated metabolism, thereby constituting a synergistic PK–PD interaction. Repaglinide is primarily metabolized by CYP3A4 and CYP2C8, whereas AN has been reported to inhibit CYP3A4.[44,45] This observation aligns with current PK evidence indicating that CYP inhibition during herb–drug co-administration can increase the plasma concentrations of conventional drugs, thereby intensifying both pharmacological and toxicological responses.[46–49] Such PK–PD concordance strengthens the hypothesis that enzyme inhibition underlies the synergistic pharmacological interaction observed *in vivo*, with possible clinical relevance regarding hypoglycemia risk under AP/AN co-administration. In contrast to these enzyme-driven interactions, certain OADs rely primarily on transporter-mediated pathways, representing the opposite end of this mechanistic spectrum.

Mechanistic insights: transporter-mediated interactions (metformin)
The reported increase in systemic metformin exposure and the enhanced antihyperglycemic response following AN pretreatment[26] jointly indicate a synergistic interaction pattern. This profile is mechanistically consistent with inhibition of OCT2/MATE-mediated renal secretion, leading to increased systemic exposure and enhanced antihyperglycemic effects. Given metformin's dependence on active renal secretion, this PK profile aligns with reduced elimination via OCT2/MATE inhibition, leading to delayed clearance and an enhanced PD response.[50,51] Comparable findings have been observed with other OCT2/MATE inhibitors, such as cimetidine and pyrimethamine, which significantly elevate metformin systemic exposure by suppressing renal secretion via OCT2 and MATE1/2-K, although the magnitude of AUC elevation varies among studies.[51–53] However, in insulin-resistant diabetic rats, the combination of purified AP extract and metformin produced a lower glucose-lowering effect than did metformin alone,[32] despite the absence of pharmacokinetic data. This apparent discrepancy may reflect differences in extract composition, treatment duration, or metabolic state (normoglycemic versus diabetic). Given the lack of PK confirmation, this antagonistic effect[32] should be interpreted cautiously as a potential PD antagonism, rather than a definitive PK–PD interaction. Collectively, these heterogeneous preclinical data highlight a context-dependent HDI: AN-rich preparations appear to enhance metformin exposure (synergistic), whereas more complex extracts may attenuate its efficacy (apparent antagonism). Clinically, such variability underscores the need for preparation type-specific evaluation and careful glucose monitoring during co-administration, given metformin's dependence on transporter-mediated elimination. At the opposite end of this continuum lies acarbose, a locally acting α-glucosidase inhibitor with negligible systemic absorption, representing the non-systemic counterpart to enzyme- and transporter-mediated interactions.

Mechanistic insights: local and non-systemic patterns (acarbose)
Regarding acarbose, preclinical findings showed that co-administration with AP or AN did not significantly alter glycemic outcomes.[35] This observation is consistent with the PK profile of acarbose, which acts locally within the intestinal lumen to inhibit α-glucosidase and exhibits negligible systemic bioavailability.[54] Similarly, while AP extracts possess α-glucosidase inhibitory activity, their systemic impact remains minimal owing to poor bioavailability.[55,56] As both agents function primarily through localized intestinal mechanisms with limited systemic exposure, the likelihood of adverse PK interactions is considered clinically negligible. Collectively, these insights suggest that non-systemic agents, such as acarbose and AP, are unlikely to exhibit meaningful HDIs that substantially alter the circulating concentrations of these medications.

Overall patterns of pharmacokinetic–pharmacodynamics interactions
The observed PK–PD alterations align with the primary clearance and transport mechanisms of each OAD examined—CYP2C9/CYP3A4 for sulfonylureas, CYP2C8/CYP3A4 and OATP1B1 for repaglinide, OCT/MATE systems for metformin, CYP3A4/5 for saxagliptin, and intestinal α-glucosidase inhibition for acarbose. This mechanistic coherence with established pharmacological pathways reinforces the internal validity of the synthesis. Overall, the direction and magnitude of HDIs involving AP or AN appear strongly context-dependent, shaped by preparation type, dosing schedule, pretreatment versus co-administration, and underlying metabolic state. This context-dependence underlies the spectrum of PK–PD patterns observed in preclinical models, encompassing synergistic interactions (enhanced exposure and effect), antagonistic interactions (reduced exposure and efficacy), and PK–PD dissociation (uncoupled changes in PK and PD).

Nonetheless, these interpretations are based on a small, heterogeneous, preclinical evidence. At the study level, the evidence is limited to a small number of preclinical rat studies with unclear risk of bias assessments; heterogeneity in AP/AN preparation, dosing regimens, treatment durations, and disease models; and incomplete reporting of paired PK and PD outcomes, which restrict opportunities for integrated PK–PD analyses. At the review level, the absence of eligible human clinical trials, the small pool of eligible animal studies, and reliance on aggregated study-level data limit clinical generalizability and preclude the assessment of within-study variability and HDI modifiers.

Practical implications
Most HDIs identified in this review were synergistic; however, notable exceptions emerged, including antagonism with glipizide under repeated AN exposure and PK–PD dissociation with tolbutamide. These divergent PK–PD patterns warrant clinical caution. Patients using AP or AN concurrently with OADs should undergo regular glucose monitoring and receive counseling to anticipate potential hypo- or hyperglycemia, consistent with regulatory and scientific guidance emphasizing systematic assessment of HDI risks and clarification of enzyme–transporter mechanisms before clinical translation.

Conclusion

Interactions between AP/AN and OADs primarily occur through CYP2C9/3A4 modulation and interference with transporter pathways (PMAT/OCT1, OCT2/MATE, and OATP1B1/P-gp), resulting in altered systemic exposure and variable glycemic responses. Across studies, the direction and magnitude of these changes varied according to preparation type (multicomponent extract versus pure compound), dose, treatment duration, metabolic status, and the dominant enzymatic or transporter pathways involved. Although most interactions exhibited synergistic PK–PD relationships, antagonistic and PK–PD dissociation patterns were also observed under specific experimental conditions, underscoring the complexity and compound-specific nature of these effects. Given the largely preclinical and heterogeneous evidence base, the current findings should be regarded as hypothesis-generating pending clinical validation. Nonetheless, this synthesis provides a mechanistic rationale for clinical vigilance, emphasizing the need for standardized preclinical models, physiologically based PK modeling simulations to delineate enzyme versus transporter contributions, and well-controlled clinical trials to confirm translational relevance and guide the safe co-administration of AP or AN with OADs.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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