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A COMPREHENSIVE REVIEW ON CANDESARTAN CILEXETIL: PHARMACOLOGICAL, PHARMACEUTICAL AND ANALYTICAL PROFILE

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ABSTRACT

Candesartan cilexetil (CAN), a prominent angiotensin II receptor blocker (ARB), has gained significant attention in cardiovascular medicine. This comprehensive review article delves into various facets of CAN, ranging from its pharmacology and pharmacodynamics to drug interactions, contraindications, and adverse reactions. The pharmacological profile of this compound is explored, elucidating its mechanism of action and its role in modulating the renin-angiotensin-aldosterone system. A detailed description of CAN, its formulation, tablet names, brand names, and compositions, is presented in a tabular format for quick reference. A crucial aspect of this review is the discussion of drug interactions, highlighting potential combinations that require caution and vigilant monitoring. Robust analytical techniques are vital for quality control, bioavailability assessment, and bioequivalence studies. Moreover, this article goes beyond clinical aspects by encompassing analytical methods employed in the quantification of CAN. The incorporation of analytical methods provides a comprehensive overview of the scientific methodologies used to measure CAN concentrations in biological samples.

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INTRODUCTION

Candesartan cilexetil is a pharmacological compound belonging to the class of angiotensin II receptor blockers (ARBs), which are widely used in the management of cardiovascular disorders. It holds a significant place in modern medicine due to its ability to effectively target the renin-angiotensin-aldosterone system (RAAS), a key regulatory pathway in maintaining blood pressure and fluid balance. By selectively blocking the angiotensin II type 1 (AT1) receptors, candesartan cilexetil exerts profound effects on vascular tone, fluid retention, and cardiovascular health. [1]

The discovery and development of candesartan cilexetil stemmed from the recognition of angiotensin II's pivotal role in controlling blood pressure, vascular resistance, and sodium-water homeostasis. Traditional antihypertensive agents focused on inhibiting the production of angiotensin II, but ARBs like candesartan cilexetil operate at a later stage in the pathway, directly antagonizing its effects. This innovative mechanism has expanded the therapeutic options for patients with hypertension, heart failure, and related conditions.

Candesartan cilexetil, through its profound impact on the RAAS, has transformed the treatment landscape for cardiovascular diseases. As we delve deeper into its pharmacology, mechanism of action, clinical applications, and potential benefits, it becomes evident that this compound has brought about substantial advancements in managing hypertension and associated complications. This introduction sets the stage for a comprehensive exploration of candesartan cilexetil's attributes and its significant contributions to contemporary cardiovascular medicine.

DESCRIPTION

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-Hydroxyethyl 2-ethoxy-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate, cyclohexyl carbonate (ester).

Its empirical formula is $C_{33}H_{34}N_6O_6$, and its structural formula is given in figure 1.

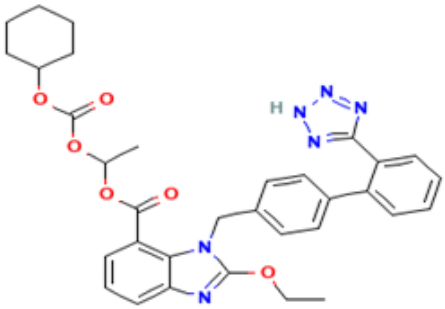

Figure 1: Chemical Structure of Candesartan Cilexetil.

Candesartan cilexetil is a white to off-white powder with a molecular weight of 610.67. It is practically insoluble in water and sparingly soluble in methanol. Candesartan cilexetil is a racemic mixture containing one chiral center at the cyclohexyloxycarbonyloxy ethyl ester group. Following oral administration, candesartan cilexetil undergoes hydrolysis at the ester link to form the active drug, candesartan, which is achiral.**[2]**

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Candesartan cilexetil operates through a sophisticated mechanism of action that involves its interaction with the renin-angiotensin-aldosterone system (RAAS), a crucial regulator of blood pressure, fluid balance, and cardiovascular function. This angiotensin II receptor blocker (ARB) exerts its effects by selectively targeting the angiotensin II type 1 (AT1) receptors, leading to a cascade of physiological responses.**[3]**

Angiotensin II Formation:

The process begins with the release of renin from the kidneys in response to various stimuli such as low blood pressure or decreased sodium levels. Renin acts on angiotensinogen, a protein produced in the liver, to convert it into angiotensin I.

Angiotensin-Converting Enzyme (ACE) and Angiotensin II:

Angiotensin I is then converted into angiotensin II through the action of angiotensin-converting enzyme (ACE), primarily located in the lungs. Angiotensin II is a potent vasoconstrictor that also stimulates the release of aldosterone from the adrenal glands.

AT1 Receptor Binding and Effects:

Angiotensin II binds AT1 receptors found in various tissues, including vascular smooth muscle cells and the adrenal cortex. Activation of these receptors leads to vasoconstriction, sodium and water retention, and stimulation of aldosterone release. These effects collectively contribute to elevated blood pressure and increased workload on the heart.

Candesartan Cilexetil Action:

Candesartan cilexetil is a prodrug, which means it undergoes conversion in the body to its active form, candesartan. Candesartan is a selective antagonist of the AT1 receptors. It competes with angiotensin II for binding to these receptors, preventing their activation. By doing so, Candesartan effectively blocks the vasoconstrictive and sodium-retaining effects of angiotensin II.

Vasodilation and Blood Pressure Reduction:

The blockade of AT1 receptors by candesartan results in vasodilation, where blood vessels relax and their resistance decreases. This leads to reduced peripheral vascular resistance, which in turn lowers blood pressure. Additionally, the inhibition of aldosterone release contributes to the reduction in fluid retention.

By disrupting the actions of angiotensin II at the receptor level, candesartan cilexetil ultimately promotes vasodilation, decreases blood pressure, and helps alleviate the strain on the cardiovascular system. Its targeted interference with the RAAS pathway has positioned it as an effective therapeutic agent in managing hypertension, heart failure, and other related conditions. [4]

PHARMACODYNAMICS

Candesartan cilexetil, a member of the angiotensin II receptor blocker (ARB) class, exerts its pharmacodynamic effects primarily by selectively antagonizing the angiotensin II type 1 (AT1) receptors. This leads to a cascade of physiological responses that contribute to its therapeutic effects in cardiovascular disorders, especially hypertension and heart failure. **[5,6]**

Angiotensin II and the Renin-Angiotensin-Aldosterone System (RAAS):

The renin-angiotensin-aldosterone system (RAAS) is a complex hormonal pathway that plays a central role in regulating blood pressure, fluid balance, and electrolyte homeostasis. One of the key components of this system is angiotensin II, a potent vasoconstrictor and stimulator of aldosterone release. Angiotensin II also promotes sympathetic nervous system activity, inflammation, and cellular growth.

AT1 Receptor Blockade:

Candesartan cilexetil selectively and competitively blocks the angiotensin II type 1 (AT1) receptors found primarily in vascular smooth muscle cells and various tissues. By binding to these receptors, candesartan cilexetil prevents angiotensin II from exerting its vasoconstrictive effects. This leads to several pharmacodynamic responses:

Vasodilation:

By inhibiting the binding of angiotensin II to AT1 receptors, candesartan cilexetil promotes vasodilation of blood vessels. This reduces peripheral vascular resistance and subsequently lowers blood pressure.

Reduction in Aldosterone Release:

Angiotensin II is responsible for stimulating the release of aldosterone from the adrenal glands. Aldosterone promotes sodium and water retention, leading to increased blood volume and higher blood pressure. Candesartan cilexetil's blockade of AT1 receptors reduces aldosterone secretion and its associated effects on fluid balance.

Inhibition of Sympathetic Activity:

Angiotensin II contributes to sympathetic nervous system activation, which can further elevate blood pressure. By interfering with this process, candesartan cilexetil indirectly dampens sympathetic activity, leading to a more balanced cardiovascular state.

Mitigation of Remodeling and Inflammation:

Angiotensin II is implicated in cardiovascular remodeling (structural changes) and inflammation. Blocking its effects through candesartan cilexetil helps to prevent detrimental alterations in the heart and blood vessels.

Clinical Implications:

Candesartan cilexetil's pharmacodynamic profile contributes to its therapeutic efficacy in managing hypertension and heart failure. By antagonizing AT1 receptors, the drug leads to vasodilation, reduced vascular resistance, and improved cardiac function. This results in lowered blood pressure, better control of fluid balance, and enhanced cardiovascular outcomes.

PHARMACOKINETICS

Candesartan cilexetil is an orally administered prodrug that undergoes biotransformation in the body to its active form, candesartan. The pharmacokinetics of candesartan cilexetil is crucial in understanding its absorption, distribution, metabolism, and elimination, which collectively determine its therapeutic effects and dosing regimen.

Absorption:

Candesartan cilexetil is rapidly absorbed from the gastrointestinal tract after oral administration. It is a prodrug that undergoes ester hydrolysis in the intestinal mucosa and liver, converting it into the active compound, candesartan. This conversion enhances its bioavailability, allowing for effective therapeutic concentrations to be achieved.

Distribution:

Candesartan, the active metabolite, exhibits a moderate volume of distribution, indicating that it is distributed throughout the body's tissues. It primarily binds to angiotensin II type 1 (AT1) receptors, thereby exerting its pharmacological effects on vascular smooth muscle and other target tissues. The protein binding of candesartan to plasma proteins, primarily albumin, is relatively high, which can influence its pharmacological activity.

Metabolism:

The conversion of candesartan cilexetil to candesartan is the primary metabolic pathway. Candesartan is minimally metabolized in the liver via glucuronidation and oxidation, resulting in the formation of inactive metabolites. Cytochrome P450 enzymes, particularly CYP2C9 and CYP3A4, are minimally involved in the metabolism of candesartan, contributing to its low potential for drug interactions mediated through these enzymes.

Elimination:

Candesartan and its metabolites are predominantly excreted via the biliary route and subsequently eliminated in feces. Renal excretion plays a minor role in the elimination of candesartan, with only a small fraction being excreted unchanged in the urine. This characteristic suggests that no dosage adjustment is necessary for patients with renal impairment.

Half-life:

The half-life of Candesartan is approximately 9 to 12 hours, indicating that it has a relatively prolonged duration of action. This extended half-life allows for once-daily dosing, contributing to improved patient adherence to the treatment regimen.

Special Populations:

In elderly individuals and those with hepatic impairment, the pharmacokinetics of candesartan may be slightly altered. However, no significant dosage adjustments are typically required based on these factors.

CONTRAINDICATIONS:

Candesartan cilexetil is a medication with specific contraindications, indicating situations in which its use is not recommended due to potential risks or adverse effects. Patients and healthcare providers should be cautious and avoid administering candesartan cilexetil under these circumstances: **[7]**

Hypersensitivity:

Individuals who have exhibited hypersensitivity reactions, including angioedema or severe allergic reactions, to candesartan cilexetil or any components of the drug should not use it.

Pregnancy:

Candesartan cilexetil should be avoided during pregnancy, especially in the second and third trimesters. Its use can adversely affect fetal development, potentially leading to fetal injury or death. Alternative medications should be considered for pregnant patients.

Breastfeeding:

Candesartan cilexetil's safety during breastfeeding has not been established. It is recommended to choose alternative treatments when nursing to prevent potential adverse effects on the infant.

Bilateral Renal Artery Stenosis:

Patients with bilateral renal artery stenosis (narrowing of both renal arteries) are at risk of acute kidney dysfunction if candesartan cilexetil is used. The drug's effects on the renin-angiotensin system can lead to reduced renal blood flow and worsen kidney function in these individuals.

Severe Renal Impairment:

Candesartan cilexetil's elimination primarily occurs through the kidneys. Therefore, individuals with severe renal impairment, including those undergoing dialysis, should exercise caution or avoid its use due to the potential for drug accumulation and adverse effects.

Severe Hepatic Impairment:

Patients with severe hepatic impairment should be closely monitored if candesartan cilexetil is prescribed. The drug's metabolism might be affected, leading to altered pharmacokinetics and potential safety concerns.

Combination with Aliskiren:

Concomitant use of candesartan cilexetil with aliskiren, a direct renin inhibitor, is generally not recommended in patients with diabetes or renal impairment. This combination may increase the risk of hypotension, hyperkalemia, and kidney dysfunction.

Pediatric Use with Reduced Renal Function:

Candesartan cilexetil's safety and efficacy have not been adequately studied in pediatric patients with significantly impaired renal function. Its use in this population should be carefully evaluated based on individual clinical considerations.

Dosage And Tolerability

Dosage The recommended starting dosage of Candesartan for most adults with high blood pressure (hypertension) is Candesartan 16 mg once a day. Based on the blood pressure response or Candesartan side effects, the dosage may be increased or decreased. With each change in dosage, it may take several weeks to see the full effects of Candesartan on lowering blood pressure. Most people require a final dose of Candesartan 2 mg to 32 mg either as one daily dose or two smaller doses. It is available in 4 mg, 8 mg, 16 mg, and 32 mg (ATACAND® product monograph).

Overdosage

No lethality was observed in acute toxicity studies in mice, rats, and dogs given single oral doses of up to 2000 mg/kg of Candesartan cilexetil. In mice given single oral doses of the primary metabolite, Candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg. The most likely manifestation of overdosage with Candesartan cilexetil would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Candesartan cannot be removed by hemodialysis.

ADVERSE REACTIONS [8,9,10,11]

Hypotension:

Candesartan cilexetil's mechanism of action involves vasodilation, which can sometimes lead to a significant drop in blood pressure, resulting in symptoms like dizziness, light-headedness, or even fainting. This is especially relevant when initiating therapy or increasing the dosage.

Hyperkalemia:

Since candesartan cilexetil affects the RAAS, there is a potential risk of elevated potassium levels in the blood (hyperkalemia), particularly in patients with impaired renal function or those taking other medications that affect potassium levels.

Renal Impairment:

In rare cases, candesartan cilexetil may contribute to impaired kidney function, particularly in patients with pre-existing kidney conditions or renal artery stenosis.

1. **Angioedema**: Although uncommon, angioedema (swelling of the deeper layers of the skin and mucous membranes) has been reported with candesartan cilexetil use. Patients with a history of angioedema or hypersensitivity reactions to ACE inhibitors should be monitored closely.
2. **Hypersensitivity Reactions**: Some individuals may experience allergic reactions, including skin rash, itching, and rarely, more severe reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.
3. **Impaired Fetal Development**: Candesartan cilexetil should not be used during pregnancy due to the risk of fetal harm or death. Pregnant patients should be switched to alternative therapies.
4. **Contraindicated in Bilateral Renal Artery Stenosis**: The drug is contraindicated in patients with bilateral renal artery stenosis, as it could lead to severe hypotension and kidney dysfunction.
5. **Other Adverse Effects**: Additional less common adverse reactions might include gastrointestinal symptoms like nausea, vomiting, and abdominal pain, as well as musculoskeletal pain and headache.
6. **Interactions with Other Medications**: Candesartan cilexetil may interact with other drugs, such as potassium-sparing diuretics, leading to further increases in potassium levels. Close monitoring and appropriate dose adjustments are crucial.
7. **Cough:** Unlike ACE inhibitors, ARBs like candesartan cilexetil are generally not associated with a persistent dry cough, a common adverse effect of ACE inhibitors.

DRUG INTERACTIONS [12,13]

1. **Potassium-Sparing Diuretics:** Concurrent use of potassium-sparing diuretics (e.g., spironolactone, amiloride) with candesartan cilexetil may increase the risk of hyperkalemia (elevated blood potassium levels). Monitoring serum potassium levels is recommended in patients with this combination.
2. **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):** NSAIDs, including ibuprofen and naproxen, can diminish the antihypertensive effects of candesartan cilexetil. Additionally, there is a potential for increased risk of kidney function impairment, especially in patients with pre-existing kidney disease. Regular monitoring of blood pressure and renal function is advised.
3. **Lithium:** Concurrent use of candesartan cilexetil and lithium (used in mood disorders) may lead to increased lithium levels in the blood. This could potentially result in lithium toxicity. Close monitoring of lithium levels is essential when these drugs are used together.
4. **Antidiabetic Agents:** Candesartan cilexetil may enhance the blood glucose-lowering effects of insulin and oral antidiabetic medications. Diabetic patients on these combinations should have their blood glucose levels closely monitored.

5. **Dual Blockade of the RAAS:** Combining candesartan cilexetil with other drugs that block the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme inhibitors (ACE inhibitors) or aliskiren, may increase the risk of hypotension, hyperkalemia, and renal dysfunction. Such combinations should generally be avoided unless carefully managed under medical supervision.
6. **Digoxin:** Candesartan cilexetil can alter the serum concentration of digoxin (used for heart failure and arrhythmias). Close monitoring of digoxin levels and clinical response is recommended when these medications are used together.
7. **Antihypertensive Agents:** Combining candesartan cilexetil with other antihypertensive agents (e.g., beta-blockers, diuretics) may lead to additive blood pressure-lowering effects. Dose adjustments may be necessary to avoid excessive hypotension.

USES

Hypertension (High Blood Pressure):

Candesartan cilexetil is prescribed to lower high blood pressure. By blocking the effects of angiotensin II, it helps relax blood vessels, reducing resistance and allowing blood to flow more easily, which ultimately lowers blood pressure.

Heart Failure:

It is also used to treat heart failure, a condition where the heart is unable to pump blood effectively, leading to fluid buildup in the lungs and other parts of the body. Candesartan cilexetil can help improve symptoms and outcomes in some heart failure patients by reducing the workload on the heart and improving fluid balance.

Prevention of Stroke:

In some cases, candesartan cilexetil might be used to reduce the risk of stroke in individuals who are at high risk due to conditions like high blood pressure and other cardiovascular risk factors.

Diabetic Nephropathy:

Candesartan cilexetil may be used to treat diabetic nephropathy, a kidney condition that can occur as a complication of diabetes. It helps slow the progression of kidney damage and reduces the risk of developing end-stage renal disease (ESRD) in certain diabetic patients.

Migraine Prevention:

Some studies have suggested that candesartan cilexetil may have a role in preventing migraines, although this is not its primary use, and further research is needed to establish its effectiveness for this purpose.**[14]**

Table-1: List of available marketed brand names for Candesartan cilexetil.

S.No.	Brand name	Composition
1	Atacand®	Candesartan cilexetil, Hydroxypropyl cellulose, polyethylene glycol, Lactose, Corn starch, Carboxymethylcellulose calcium, and Magnesium stearate.
2	Blopress®	Candesartan cilexetil and hydrochlorothiazide
3	Amias®	Candesartan cilexetil, lactose monohydrate
4	Candesar®	Candesartan Cilexetil, Lactose monohydrate, croscarmellose sodium, microcrystalline cellulose
5	Cantar®	Candesartan Cilexetil, Mannitol, hydroxypropyl cellulose, magnesium stearate
6	Kenzen®	Candesartan cilexetil, Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate.
7	Ratacand®	Candesartan cilexetil, Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate.
8	Candelong®	Candesartan cilexetil, Lactose monohydrate, hydroxypropyl cellulose, magnesium stearate, maize starch

Table-2: List of analytical methods reported for Candesartan cilexetil.

S. No.	PARAMETERS		RESULT	
Method: TLC				
1 **[15]**	System	A Shimadzu (Kyoto, Japan	Linearity	1.0-9.0 µg/spot
	Column	TLC aluminum plates (20×20 cm) precoated with a 0.25 mm layer of silica gel 60 F254 were purchased from Merck (Darmstadt, Germany)	R^2	0.9996
	Mobile phase	Ethyl acetate-methanol-toluene-ammonia solution	LOD	0.02 µg/spot
	Flow rate	0.75 ± 0.02 cm/min	LOQ	0.07 µg/spot
	Sample volume	0.8 µL		
	Detector	UV lamp detector		

	Detection wavelength	254 nm		
Method: HPTLC				
	System	Perkin-Elmer Lambda Ez201		
	HPTLC Plate	HPTLC plate (20×10 cm. aluminum plates with 250 µm thickness protected with silica gel 60 F254) E. Merck (Darmstadt, Germany)	Rf value	0.74
2 [16]	Mobile phase	Separation was carried out on Merck HPTLC aluminum sheet of silica gel 60 F254 using chloroform: methanol (8:2, v/v)	LOD	3:1
	Detector	Perkin -Elmer Lambda EZ201 UV visible spectrophotometer	LOQ %RSD	10:1 10%
Method: HPLC				
	System	Alliance Water separation module 2695		
	Column	Kromasil 100 C18 column (4.6mm i.d × 25 cm length, 5 µm particle diameter)	Linearity range	16-200 ng/ injection
	Column temperature	25 ± 2^0 C		
3	Mobile phase	Acetonitrile and 0.02 M Sodium acetate	LOD(%RSD)	Less than 6%
[17]	Flow rate	1 mL/min	Recovery range	101.6-98.3%
	Injection volume	10 µL		
	Detector	Water 2996 Photodiode array detector (Milford, M., USA)		
	Detection wavelength	265 nm	Accuracy and precision	Less than 1.8%
	System	Shimadzu LC- 10AT System used	Linearity range	0.5-400 µg/mL
	Column	Hypersil ODS C-18 (250 × 4.6 mm, packed with 5 microns)	Retention time	3.025 min
	Mobile Phase	Acetonitrile:0.05 M KH2PO4 buffer	LOD	0.358 µg/mL
4	Flow Rate	1.5 mL/min (Gradient)	LOQ	1.196 µg/mL
[18]	Injection volume	20 mL	%RSD	0.3058 %
	Detector	UV detector		
	Detection wavelength	256 nm		
	System	Agilent 1100 HPLC System	Linearity	25-200 µg/mL
	Column	Kromasil C18 column (250 × 4.6 mm; 5µ)		
	Column temperature	30^0C		
5	Mobile phase	Water, acetonitrile, and trifluoro acid in the ratio of 48: 52: 0.1 v/v)	Retention time	5.54 min
[19]	Flow rate	1.5 mL/min	R^2	1
	Injection volume	10 µL		
	Detector	Photodiode-array detector		
	Detection wavelength	240 nm	% RSD	0.4 %
	System	Perkin Elmer series Binary LC pump, Model 200B/250	Linearity	50-5000 ng/mL
	Column	A Phenomenex Luna C8, 250×4.6 mm, 5µ column	R^2	0.9997
6	Mobile phase	Eluent mixture of Methanol-10mM potassium dihydrogen phosphate (pH 3.0) with the composition of (85:15 v: v)	LLOD	20 ng/mL
[20]	Flow rate	1.0 mL/min	LLOQ	50 ng/mL
	Detector	Ultraviolet detector	Run time	7 min
	Detection wavelength	260 nm		
	System	Agilent Technology -1100 series liquid chromatography	Linearity	4.0-12 µg/mL
	Column	C18(Prodigy,150×4.6 mm 5µ)	%RSD	Not more than 2%
7	Mobile phase	A mixture of 0.02M mono potassium phosphate buffer: Acetonitrile: triethyl amine in the ratio of 40:60:0.2 and adjusted the pH to 6.0 with phosphoric acid		
[21]	Flow rate	1 mL/min		
	Injection volume	20 µL		
	Detector	G1314 A Multiwavelength detector		
	Detection	254 nm		

	wavelength			
	System	HPLC consisted of a Water 600 controller		
	Column	Chromolith RP-18e column		
	Column temperature	20℃		
8 [22]	Mobile phase	Acetonitrile – 0.1% trifluoroacetic acid aqueous solution in ratio 50.0: 50.0 (v/v) in an isocratic elution	%RSD	Less than 6%
	Flow rate	1.5 mL /min		
	Detector	Waters 996 photodiode array detector		
	Detection wavelength	251 nm		
	System	Shimadzu uv-1700 visible spectrophotometer using 10 mm matched cuvettes	Linearity range	10-60 µg/mL
	Column	Phenomenex, Luna 5µ C18, 100A, 250×4.6mm	Retention time	2.150 min
	Column temperature	room temperature	Concentration range	0.0100 AUFS
9	Mobile phase	MeOH: CAN: 5mM potassium dihydrogen phosphate (75:20:4 v/v/v)	LOD	500 ng/mL
[23]	Flow rate	1mL / min	LOQ	1 µg/mL
	Injection volume	20 µL	Theoretical plates	1931.92
	Detector	Shimadzu Liquid with UV-visible detector	R^2	0.9997
			Run Time	10 minutes
	Detection wavelength	260 nm	%RSD	0.3043%
	System	Agilent Technology HPLC model containing the pump		
	Column	Kromacil C18, column 5 µm (150mm × 4.6 mm)		
	Column oven temperature	30^0C		
10	Mobile phase	Buffer (pH 4.5) and acetonitrile	Run time	10 min
[24]	Flow rate	1.5 mL/min		
	Injection volume	50 µL		
	Detector	Variable wavelength programmable UV/visible detector		
	Detection wavelength	UV at 257 nm		
	System	Shimadzu HPLC instrument (LC-10AT Vp)	Linearity range	0.8-80 µg/mL
	Column	Hiber 250 × 4.6 mm Lichrospher 100 C18 column (250 mm × 4.6 mm i.d., 5 µm particle size)	Retention time	8.100 min
11	Mobile phase	0.01 M Tetra butyl ammonium hydrogen sulfate (pH 3.37) and methanol (15:85 v/v)	LOD	0.1892 µg/mL
[25]	Flow rate	1 mL/min	LOQ	0.6187 µg/mL
	Injection volume	20 µL	R^2	0.999
	Detector	UV-Visible detector	% RSD	0.31 %
	Detection wavelength	270 nm		
	System	SHIMADZU-SPD20A HPLC system	Linearity	1-30 µg/mL
	Column	PHENOMENEX – C8 (250 mm × 4.6 mm, 5 µm)	R^2	0.999
	Mobile phase	acetonitrile: Buffer (Heptane sulphonic acid)	Retention time	4.95 min
12	Flow rate	1 mL/min	LOD	600 µg/mL
[26]	Injection volume	10 µg/mL	LOQ	300 µg/mL
	Detector	SPD-M20A PDA detector		
	Detection wavelength	230 nm	% RSD	1.44 %
	System	The Shimadzu model and software used were of LC-Solution	Linearity range	10 – 500 µg/mL
	Column	C18 (Kromasil, ODS, 5 µ, 250 × 4.5 mm) column	LOD	3.1 µg/mL
13 [27]	Mobile phase	Methanol-acetonitrile-disodium hydrogen phosphate (0.01 M; pH adjusted to 2.5 with orthophosphoric acid)	LOQ	10 µg/mL
	Flow rate	1 mL/min	Retention time	5.89 min
	Detector	UV detector	R^2	0.998
	Detection	240 nm		

	wavelength			
14 [28]	System	RP-HPLC Agilent 1200 series quaternary pump (DE62974693)	Retention time	2.2 min
	Column	Agilent, Zorbax C18 column (150mm × 4.6mm, 5 µm)	Linearity	2.0-20.0 mcg/mL
	Mobile phase	Phosphate buffer (pH 2.5)-acetonitrile (15:85, v/v)	R^2	1.0
	Flow rate	1.0 mL/min	% RSD	1.8 %
	Injection volume	20 µL	LOQ	1 mcg/mL
	Detector	Hanna pH analyzer (Microprocessor pH 211)		
	Detection wavelength	215 nm		
15 [29]	System	HPLC system (waters 1525) is composed of binary HPLC pump	Linearity	0.5-1 µg/mL
	Column	RPC Sunfire C18 analytical column (250 × 4.6 mm × 5µm)	Retention time	14.5 min
	Mobile phase	Acetonitrile: sodium dihydrogen phosphate (adjusted to pH 2.6 using orthophosphoric acid)	LOD	1.39 µg/mL
	Flow rate	1 mL/min	LOQ	4.64 µg/mL
	Injection volume	20 µL	R^2	0.999
	detector	Water 2487 dual wavelength absorbance detector		
	Detection wavelength	238 nm		
16 [30]	System	HPLC system (Shimadzu, Kyoto, Japan)	Linearity range	0.25-8 µg/mL
	Column	Onyx monolithic C18 column (Phenomenex, 100 mm^2 4.6 mm i.d, particle size 5µ)		
	Column temperature	25^0C		
	Mobile phase	20 mM phosphate buffer pH adjusted to 4.0 with OPA and acetonitrile	Retention time	3.8 and 7.0 min
	Flow rate	1 mL /min	R^2	0.9997
	Injection volume	20 µL		
	Detector	LC-20AD UV detector		
	Detection wavelength	254 nm	%RSD	<2%
17 [31]	System	Agilent Technologies HP 1200 series having UV detector and autosampler (USA)	LOD	3.3 σ/S
	Column	(250 × 4.6 mm, 5 µm particle; Clipeus, Higgins Analytical Inc., USA)		
	Column temperature	25℃		
	Mobile phase	25℃ A mixture of 0.05 M phosphate buffer, pH 4.5, and methanol (40:60, v/v) adjusted to Ph 4.0 with trifluoroacetic acid	LOQ	10 σ/S
	Flow rate	1.0 mL/min	RSD	0.041%, 0.202%
	Injection volume	20 µL		
	Detection wavelength	254 nm		
	Particle size	5 µm		
18 [32]	System	HPLC pump, LC-10AT VP with fluorescence detector	Linearity	3.125ng/mL – 200ng/mL
	Column	C- 18 HPLC, column particle size (5 µm) Mediterranean Sea L × 1.D. 25cm×4.6mm (Supelcosil)	Retention time	6±0.5 min
	Mobile phase	Acetone, diethylamine, and distilled water	R^2	0.99
	Injection volume	30 µL	% RSD	±15%
	Detector	247 nm using a fluorescence detector	LLOQ	3.125ng/ml
	Detection wavelength	392nm	Run time	1.1 v/v
19 [33]	System	Shimadzu model LC 2010 CHT, UV	Retention time	10.6 min
	Column	A reversed-phase analytical column, Inertsil ODS 3V (250 × 4.6 mm, 5 µm)	LOD	0.20 µg/g
	Column temperature	25^0C	LOQ	0.58 µg/g
	Mobile phase	Water and acetonitrile	% RSD	2.32 %

	Flow rate	1.0 mL/min	R^2	0.9998
	Injection volume	30 µL	Run time	20 min
	Detector	Photodiode array detector		
	Detection wavelength	364 nm		
	System	Shimadzu Corporation (Kyoto, Japan)	Linearity range	0.10 – 80 µg/mL
	Column	YMC Pack AM12S05 ODS (150 mm × 6 mm I.D., particle diameter of 5 µm)		
	Column temperature	40^0C		
20 **[34]**	Mobile phase	acetonitrile-water-perchloric acid (60%)-sodium perchlorate monohydrate	Retention time	8.8 min
	Flow rate	1 mL/min	R^2	0.99999
	Injection volume	20 µL		
	Detector	Model SPD-20A UV spectrophotometric detector		
	Detection wavelength	254 nm	LOQ	0.10 µg/mL
	System	Agilent Technologies 1220 II HPLC system	Linearity range	4-24 µg/mL
	Column	Kromasil C18 (150 × 4.6 mm, 5 µm) column		
	Column temperature	30^0C		
21 **[35]**	Mobile phase	60% 20 Mm Potassium dihydrogen orthophosphate and 40% acetonitrile v/v), isocratic elution pattern	LOD	0.51 µg/mL
	Flow rate	0.9 mL/min	LOQ	1.56 µg/mL
	Injection volume	10 µL		
	Detector	UV detector	R^2	0.9997
	Detection wavelength	220 nm	%RSD	<1%
Method: LC-MS/MS				
	System	A Shimadzu LC-10A system	Linearity	5-45 µg/mL
	Column	250mm × 4.6mm i.d, 5µL particle, Hypersil (UK) Phenyl 2 column	LOD	0.08 µg/mL
22 **[36]**	Mobile phase	25:75:0.2 mixture of 0.02M potassium dihydrogen phosphate, methanol, and triethylamine, final pH 6.0 ± 0.1	LOQ	0.9 µg/mL
	Flow rate	1 mL/ min		
	Injection volume	20 µL		
	Detector	SPD-10A Variable wavelength detector		
	Detection wavelength	271 nm		
	System	YL9100 HPLC System (Young Lin Instrument, Anyang, Korea	Linearity range	32-160 µg/mL
	Column	An RP-18 column (125mm× 4mm,5 µm)		
	Mobile phase	Acetonitrile and water with acetic acid and triethylamine (pH 4.1)	% RSD	Below 3.0%
23 **[37]**	Flow rate	1 mL/ min		
	Injection volume	20 µL	Recovery	Between 98.1% and 103.9%
	Detector	Photodiode array detector (DAD)		
	Detection wavelength	225 nm	LOD	0.55 and 0.67 µg/mL
			LOQ	1.66 and 2.00 µg/mL
	System	Shimadzu HT (Shimadzu, Japan) LC System	Linearity	1.080 ng/mL
	Column	Zorbax Eclipse XDB-C18 4.6 × 150 mm, 5µm (Make: Agilent Technologies)	Retention time	1.10±0.1 min
	Mobile phase	HPLC grade acetonitrile: 5mM ammonium acetate in water (75:25, v/v)	R^2	0.99
24 **[38]**	Rinsing solution	HPLC grade acetonitrile: milli-Q water or HPLC grade water (60:40, v/v)	%RSD	<20%
	Flow rate	1.0 mL/min		
	Split ratio	50:50		
	Sample cooler temperature	10^0C		

	Injection volume	15 µL		
	Needle rinsing Volume	500 µL		
	Column oven temperature	N/AP		
	Rinsing mode	Before and After aspiration		
	System	Waters Alliance 2695 LC system (Waters Corporation, Milford, MA, USA)		
	Column	Purosphere Star RP18e column of 150 × 4.6 mm I,d packed with 5 µm particle size		
25 **[39]**	Mobile phase	Solvent A acetonitrile-ammonium acetate (pH 5.0; 20 mM) (10:90 v/v) Solvent B acetonitrile-ammonium acetate (pH 5.0; 20 mM) (90:10 v/v)		
	Flow rate	1.2 mL/min		
	Detector	2996 photodiode array detector		
	Detection wavelength	254 nm		
Method: UPLC				
	System	Water Accquity binding pump plw auto sample		
	Column	Zorbax Extended C18(50×4.6 mm) with 1.8µm particles	Linearity ranges	250,375,500,750 and 100 µg/mL
	Column Temperature	40^0 C		
	Mobile phase	(A) .0.1% Triethyl Amine in water pH-2.2 with TFA (B) . 0.1% TFA in Acetonitrile and water in the ratio (95:5)		
26 **[40]**	Concentration	1.0 mg/mL	Retention time	270 min
	Flow rate	0.4 mL/min		
	Injection volume	5 µL	LOQ(%RSD)	5.2%
	Detector	Photodiode array detector	Run time	1 min
	Detection wavelength	210 nm		
	System used	UPLC apparatus (Acquity Waters, UK)		
	Column	C8 column (ACQUITY UPLC BEH C8, 1.7 µm, 100 × 2.1 mm, UK)		
	Column temperature	35 ± 0.5^0C		
	Mobile phase	A 0.01 M phosphate buffer at pH 3.0 B 100% acetonitrile		
27 **[41]**	Flow rate	0.5 mL/min		
	Injection volume	10 µL		
	Detector	UV detector		
	Detection wavelength	304 nm		
	Concentration range	99.99-100.00 ± 0.011%		
	System	AcquityUPLC (Waters, Milford, MA, USA) with a Xevo TQ-MS+ triple quadrupole tandem mass spectrometer (waters)	Linearity	2-500 ng/mL
	Column	Thermo Hypersil Gold C18 column (150×2.1 mm, 1.9µm)	Retention time	0.4 min
28 **[42]**	Column temperature	40^0C	LLOQ	2 ng/mL
	Mobile phase	5mM ammonium formate and acetonitrile	Run time	0.9 min
	Flow rate	0.4 mL/min		
	Injection volume	3 µL		
	Detector	Electrospray ionization positive mode with multiple reaction monitoring		
	System	Waters Aquity UPLC system	Linearity	2.0-20.0 µg/cm^3
	Column	(50 mm×2.1 mm, 1.7µm		
29 **[43]**	Column temperature	29^0C	LOD	0.55 µg/cm
	Mobile phase	Methanol and Britton -Robinson (B-R) buffer (pH=2.0)		

		(81:19, v/v)		
	Flow rate	0.3 mL/min		
	Injection volume	4 µL	LOQ	1.84 µg/cm
	Detector	PDA detector	Concentration range	2.0-20.0 µg/cm^3
	Detection wavelength	270 nm	Retention time	1.23 min
	System	Waters AQUITY UPLC system		
	Column	ACQUITY HSS T3 column (2.1 mm × 50 mm, 1.8 µm; Waters)		
	Column temperature	45^{0}C		
30 **[44]**	Mobile phase	A Water with 0.1% formic acid B CAN-MeOH (9:1, v/v) with formic acid (gradient elution)		
	Flow rate	0.5 mL/min		
	Injection volume	2 µL		
	System	ACQUITY UPLC H-Class (Waters, Milford, MA, USA)		
	Column	ZORBAX Eclipse Plus RRHD C18 column (5 cm × 2.6 mm, 1.8 µm)	Linearity Range	1-240 µg/mL
	Column temperature	30^{0}C		
	Mobile phase	A: Purified water-acetonitrile-glacial acetic acid (95:5:0.1, v/v)	LOD	0.20 µg/mL
31 **[45]**		B: Purified water-acetonitrile-glacial acetic acid (5:95:0.1, v/v)		
	Flow rate	0.4 mL/min		
	Injection volume	10 µL	LOQ	0.61 µg/mL
	Sample cooler temperature	15^{0}C		
	Detector	Photodiode array (PDA) detector	%RSD	≤2.0%
	Detection wavelength	265 nm	Run time	4.5 min
	System	Waters-Acquity UPLC system		
	Column	Acquity UPLC HSS T3, 100 × 2.1 mm with 1.8 µm particle size column		
	Column temperature	45^{0}C		
32 **[46]**	Mobile phase	A 0.1% Perchloric acid in water B acetonitrile		
	Flow rate	0.5 mL/ min (Gradient elution)		
	Injection Volume	4 µL		
	Detector	Photodiode array detector		
	Detection wavelength	220 nm		
	Method: UPLC-MS/MS			
	System	Agilent UHPLC unit (Agilent Corporation, MA, USA)		
	Column	ZORBAX Eclipse Plus C18 column (1.8 µm, 2.1 × 50mm, I.D. Agilent Corporation, MA, USA)		
33 **[47]**	Column temperature	30^{0}C		
	Mobile phase	Acetonitrile: distilled water (85:15 v/v)		
	Flow rate	0.2 mL/min		
	Detector	Agilent 6420 triple-quadrupole mass spectrometer		
	Retention time	2.1 min		
	System	ACQUITY TQD Waters, Milford, MA, USA	Linearity range	10.01 – 500.43 ng/mL
34 **[48]**	Column	ACQUITY UPLC C18 1.7 µm, 2.1 × 50 mm	R^2	0.9999
	Mobile phase	acetonitrile and formic acid	LOQ	10.01 ng/mL
	Flow rate	0.2 mL/min		

Detector	Tandem mass spectrometer detector

CONCLUSION

This review article has successfully synthesized a wealth of information about candesartan cilexetil, offering valuable insights for both clinical application and further research endeavors. Its comprehensive coverage of the drug's various facets contributes to the holistic understanding of its pharmacological properties, potential interactions, and analytical assessment, ultimately enhancing the knowledge base for improved patient care and drug development.

ABBREVIATIONS:

Candesartan cilexetil (CAN)
Angiotensin II receptor blocker (ARB)

CONFLICT OF INTEREST

All the authors have no conflict of interest.

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