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Review Article

NIFEDIPINE'S SYNERGISTIC THERAPEUTIC POTENTIAL: OVERCOMING CHALLENGES AND EMBRACING NOVEL APPLICATIONS IN PHARMACOTHERAPY

Muneeb Ur Rahman[1]*, Hafiz Rashid Hussain[1], Habiba Akram[2], Faisal Gulzar[3], Muhammad Nouman[1], Hassan Farooq[1], Arslan Ashfaq[1], Zaha Kalsoom[1]

[1]*College of Pharmacy, University of Sargodha, Sargodha 40100, Pakistan*

[2]*Department of Pharmacy, University of Agriculture, Faisalabad 38000, Pakistan*

[3]*College of Pharmacy, Rai Institute of Medical Sciences, Sargodha 40100, Pakistan*

* Correspondence, e-mail: muneeb.rahman.pharmd@gmail.com

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ABSTRACT

Nifedipine (NIFE) is a potent first-generation dihydropyridine calcium channel antagonist that belongs to the BCS-II drug. It inhibits calcium entry through L-type channels and disrupts the Ca-calmodulin complex, which ultimately blocks myosin light chain kinase activation, resulting in vasodilation, reduction in blood pressure, and negative chronotropic effect, thus slowing the heart rate. NIFE was used in the treatment of hypertension and angina. However, physicochemical properties, pharmacokinetic profile, mechanism of action, and therapeutic efficacy explain the widespread use of medication in various medical conditions. With a primary focus on its calcium channel-blocking properties, NIFE has demonstrated therapeutic efficacy in addressing classical vasospastic disorders, such as Raynaud's phenomenon, by modulating vascular function and reducing the episodes of digital ischemia. NIFE has been proven beneficial in ureteral stones by increasing their passage rates and in migraine by producing vasodilation. NIFE exhibits therapeutic effects by inhibiting proliferation and metastasis in colorectal cancer through reactivating tumour immunity. Similarly, it has great potential in obstetrics, as it effectively manages preterm labor by delaying the delivery and optimizing fetal conditions. Moreover, its applications can expand into evolving domains, such as achalasia, glaucoma, and chilblains, and potentially as an effective intervention against COVID-19.

KEYWORDS: Ca Channel Blocker; Nifedipine; Colorectal Cancer; Migraine Therapy; Raynaud Phenomenon

1. Introduction

According to the biopharmaceutics classification system (BCS), NIFE belongs to class BCS-II [1], which has low solubility and high permeability. It is a potent calcium channel antagonist chemically known as first-generation dihydropyridine [2,3]. Moreover, NIFE is beneficial in treating cardiovascular conditions such as hypertension, angina, hypertrophic obstructive cardiomyopathy, and infectious endocarditis. In some cases, it can treat spasticity in children aged [4-6]. The molecular structure of NIFE is shown in Fig. 1.

German pharmaceutical company Bayer first manufactured NIFE in 1966 [7]. Later on, various investigations have shown that NIFE can improve coronary blood flow at very low doses and effectively avoid angina episodes in patients, especially those with variant types of the disease. Hence, it can also manage hypertension [8,9]. NIFE was granted FDA approval in 1981 and was first introduced for clinical use in Germany in 1982 [10].

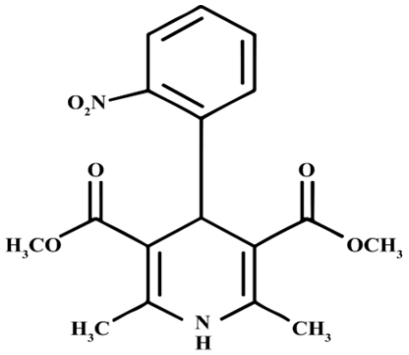

Fig. 1. Structure of complex organic compound nifedipine, NIFE, consists of a benzene ring, a central core including carbon, nitrogen, and oxygen atoms, and several functional groups, including an amine group, two ester groups, and a nitro group.

The clinical application of NIFE extends beyond its traditional therapeutic uses, as it mimics peripheral resistance by promoting oxygen supply to deprived cells or tissues. This increases cardiac output and minimizes the cardiac workload, thus preventing patients from going into medical emergencies; this makes NIFE a highly beneficial therapeutic moiety [11-13].

Despite well-established medical advantages, there remains a significant concern about its bioavailability and solubility, which limits its use to some extent [14]. Still, recent advances in drug delivery systems, such as the development of controlled-release formulations, have overcome this limitation and come up with better therapeutic outcomes, making it an even more beneficial agent to treat cardiovascular and other diseases [15].

Considering its utilization and efficiency, NIFE is one of the most used therapeutic agents for cardiovascular diseases and ongoing research, particularly optimizing its pharmacokinetics and exploring its novel application in various unmet health conditions [16].

1.1. Physicochemical properties

The physicochemical properties of NIFE are listed in Table 1.

Table 1. Physicochemical profile of nifedipine: molecular formula, weight, melting point, solubility, pKa value, and crystallinity.

Property	Description	Ref.
Molecular formula	$C_{17}H_{18}N_2O_6$	[17]
Molecular weight	346.3 g·mol^{-1}	[17]
Melting point	171–175 °C	[7,18]
Standard molar enthalpy	144.8 kJ·mol^{-1}	
Solubility	Poorly soluble in water (436.3 mg/L); better solubility in ethanol, methanol, and chloroform	[19]
pKa value	Approximately 3.93, indicating weak acidity	[20]
Crystallinity	Crystalline; structure studied using X-ray crystallography	[21]

1.2. Mechanism of action

Calcium ions enter via calcium channels in the blood vessels, constricting or narrowing the vessels and leading to high blood pressure [22]. Furthermore, the entry of calcium ions through the sinoatrial (SA) node, the body's natural pacemaker, starts a normal heartbeat in the cardiac cells [23]. After entry through L-type calcium channels, calcium binds with calmodulin (a calcium modulator protein) to form a Ca-calmodulin complex responsible for the contraction of vascular smooth muscles [24]. This complex subsequently acts on the phosphorylating enzyme myosin light chain kinase (MLCK) and activates it. The activated MLCK phosphorylates myosin light chain (MLC) at their regulatory site, forming a complex with actin (actomyosin complex), responsible for the contraction of vascular smooth muscles [25] as shown in Fig. 2.

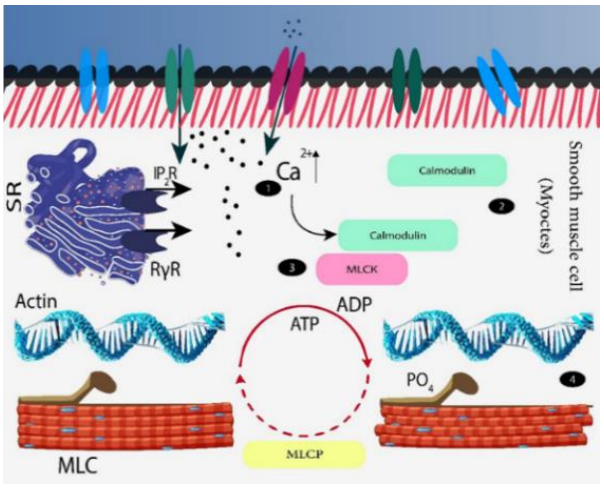

Fig. 2. Illustration shows the movements of calcium ions (Ca^{2+}) and associated physiological processes in smooth muscle cells. The entry of Ca^{2+} ions proceeds via receptor-operated channels (ROC), store-operated channels (SOC), and voltage-dependent calcium channels (VDCC) that are integrated into the cell membrane. The possibility of a subsequent influx of Ca^{2+} ions is also shown. The sarcoplasmic reticulum (SR) releases Ca^{2+} ions within the cell in response to inositol trisphosphate (IP3) activation. The ryanodine receptor (RyR), a sarcoplasmic reticulum (SR) component, releases calcium ions. The interaction between actin filaments and myosin light chain (MLC) emphasizes the involvement of ATP in releasing energy and phosphate (PO_4^{3-}) during myosin activation. The interaction between calmodulin and Ca^{2+} leads to myosin light chain kinase (MLCK) activation, activating myosin light chain (MLC) for contraction.

NIFE blocks the voltage-gated L-type calcium channels in the blood vessels and the SA node and slows calcium entry into these cells [26]. Inhibition of calcium entry into these cells during depolarization prevents the narrowing of the blood vessels and promotes dilatation of peripheral and coronary blood vessels. Moreover, dilation of blood vessels assists in reducing blood pressure and also improves blood flow, reducing the workload on the heart. Reduced workload on the heart enhances cardiac function efficiency in individuals with angina and other related cardiovascular diseases [27–29], as shown in Fig. 3.

1.3. Pharmacokinetic Profile

Pharmacokinetics parameters such as absorption, distribution, metabolism, and excretion [30] of NIFE from the body are described in Table 2.

1.4. Therapeutic Efficacy

Numerous dose-ranging and comparative studies have investigated the therapeutic efficiency of calcium channel blockers in individuals with various degrees of angina, arrhythmia, and hypertension [39,40]. The clinical efficacy of NIFE is linked with its ability to reduce systolic or diastolic blood pressure due to its potent vasodilatory effect on smooth muscles with minimal impact on heart contractility, owing to its balanced pharmacodynamic profile [10,41]. NIFE's developments as a sustained-release formulation make it a more prescribed agent for chronic, life-threatening cardiovascular diseases such as angina. However, careful supervision is required to minimize the potential adverse reactions and optimize therapeutic effects [8,9].

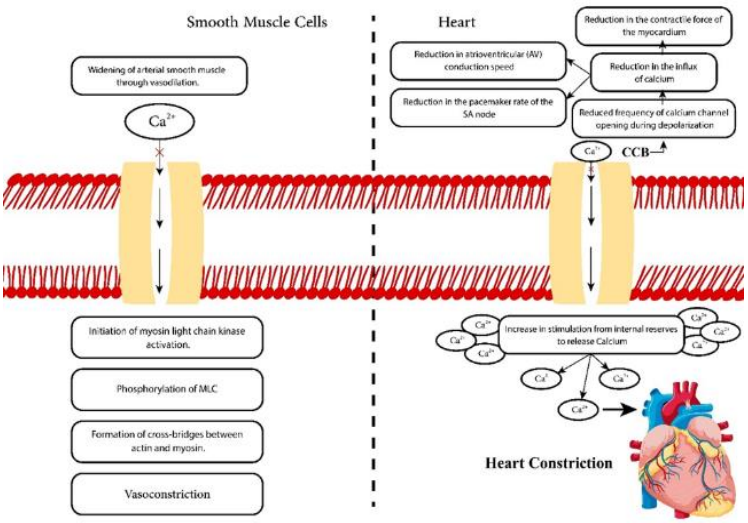

Fig. 3. The function of calcium ions in the contraction of smooth muscle and the heart. The diagram shows the complex mechanisms associated with the contraction of smooth muscle cells and the heart, emphasizing the crucial involvement of calcium ions. To the left, there is a sequence illustrating the role of calcium ions in causing vasoconstriction in smooth muscle cells. The process begins with the dilation of arterial smooth muscle by activating myosin light chain kinase, which leads to phosphorylation and cross bridges between actin and myosin. This ultimately causes vasoconstriction. On the flip side, there is a detailed illustration of cardiac contraction on the right side. Calcium ions also have a vital function in this context; their decrease in the sarcoplasmic reticulum layer reduces their release rate when depolarization occurs. This effect is linked to a decrease in the frequency of calcium channel opening during depolarization. Calcium ions are crucial in smooth muscle cell and heart contractions, highlighting their significance in muscular contractions across many cell types at a cellular level.

Table 2. Pharmacokinetics processes of nifedipine in a human showing how it is absorbed, distributed, metabolized, and excreted from the body. Moreover, pharmacokinetic parameters are indicated, ultimately influencing the pharmacological agent's therapeutic efficacy of nifedipine.

Parameter	Value /Range	References
	Absorption	
Bioavailability	Variable, approximately 40-50%	[31]
Food affects	Should be taken on an empty stomach or with a light meal	[31]
	Distribution	
Protein binding	71.79-89.15% /1200 ng ml-1	[32]
Volume of Distribution	Approximately 2-3 L/kg.	[33]
Placental transfer	Readily crosses the placenta	[34]
Breast milk excretion	Excreted into breast milk.	[35]
	Metabolism	
Metabolic pathway	CYP3A4 predominantly metabolizes it	[36]
Metabolites	2,6-dimethyl-4-(2-nitrophenyl)-5-methoxycarbonyl-pyridine-3-carboxylic acid 2-hydroxymethyl-pyridine carboxylic acid Dehydronifedipine	[37]
	Excretion	
Elimination Half-life	2-4 hours (can be prolonged in hepatic impairment).	[37]
Clearance	450-700 mL/min	[38]
Route of excretion	Primarily in urine and faeces.	[38]
Factors Influencing PK	Age, gender, renal and hepatic function, co-administration of CYP3A4 inhibitors/inducers.	

1.5. Indications

1.5.1. Angina pectoris

NIFE treats chronic, stable angina caused by chronic artery disease (CAD) in combination with other anti-anginal medications owing to its vasodilatory effect, i.e., by improving oxygen supply to the heart and reducing its workload [42].

1.5.2. Hypertension

NIFE is used to treat hypertension either alone or in conjunction with other drugs (such as ACE inhibitors, thiazide diuretics, and ARBs) [2]. Moreover, indirect cardio-stimulation results from vasodilation and a rise in sympathetic tone regulated by baroreceptors, particularly in individuals with severe hypertension [26].

1.6. Adverse effects

NIFE is generally considered safe and well-tolerated. However, like all medications, it can cause some toxic effects in some patients [42]. Adverse effects are characterized as most common or idiosyncratic and extremely rare, as shown in Table 3.

Table 3. Nifedipine's most common and rare Adverse Drug Reactions

Most common side effects	Idiosyncratic/rare side effects	Ref.
Hypotension	Urticarial rashes	[43,44]
Dizziness	Gingival hyperplasia	[45,46]
Flushing	Arthralgia	[47,48]
Headache & nausea	Acute kidney injury	[7,47,49]
Bradycardia	Hepatotoxicity	[43,50]
Palpitation	Parkinsonism in old age	[51,52]
Peripheral edema	Ejaculatory dysfunction in man	[7,53]
Constipation		[46]

1.7. Contraindications

NIFE administration involves absolute and relative contraindications, which should be carefully considered in clinical practice. Absolute contraindications include myocardial infarction with ST-elevation, where NIFE use may worsen myocardial ischemia or hypersensitivity reactions to the drug or any of its ingredients [54,55]. Severe aortic stenosis, unstable angina, hypotension, heart failure, and moderate to severe hepatic impairment are instances of relative contraindications. Because of safety concerns, immediate-release NIFE formulations are not recommended in hypertensive emergencies. This is especially true in the case of cardiogenic shock, wherecardiac function may be further compromised by calcium ion suppression [56]. Hypotensive individuals may encounter worsened hypoperfusion as a result of NIFE use, whereas patients who have hepatic dysfunction are more vulnerable to toxicity because of compromised drug metabolism. When prescribing NIFE in clinical settings, these factors highlight the importance of risk assessment and customized treatment plans [57,58].

1.8. Drug Interactions

NIFE can interact with other medications, potentially leading to increased or decreased levels of NIFE and potentially increasing the risk of adverse effects [59]. Significant NIFE interactions are shown in Table 4.

1.9. Dosage

The dosage of NIFE depends on the condition being treated and other patient factors such as age, weight, and overall health [66]. Here are some general guidelines for the dosage of NIFE shown in Table 5.

Table 4. Interactions between various substances (such as CYP3A4 inhibitors, CYP3A4 inducers, beta-blockers, digoxin, cyclosporine, and grapefruit juice) and nifedipine, a calcium channel blocker medication, and their effects, as reported in various studies

Interactions	Effect on Nifedipine	References
CYP3A4 inhibitors	Increase nifedipine blood levels	[60]
CYP3A4 inducers	Decrease nifedipine blood levels	[60]
Beta-blockers	Decrease nifedipine blood levels, potentially reducing efficacy	[61]
Barbiturates	Decreased effects of nifedipine	[62]
Digoxin	Decrease nifedipine blood levels, potentially reducing efficacy	[63]
Cyclosporine	Decrease nifedipine blood levels, potentially reducing efficacy	[64]
Cimetidine	Increased effects of nifedipine	[62]
Grapefruit juice	The use of NIFE in these patients should be avoided because of their potential to worsen myasthenia symptoms	[46]
Myasthenia gravis	The use of NIFE in these patients should be avoided because of their potential to worsen myasthenia symptoms	[65]

Table 5. Recommended doses of nifedipine for various medical conditions

Condition	Recommended dose	References
Hypertension	30 mg once daily (can be increased to 60-90 mg as needed)	[67]
Angina	Three times a day, 10–20 mg for immediate release 30 or 60 mg daily for extended-release	[67]
Vasospastic angina	30 or 60 mg daily for extended-release	[67]
Raynaud's phenomenon	If needed, 10 to 30 mg daily and increase to long-acting (XL) to a maximum of 90 mg daily	[68]
Pre-term labor	Oral loading dose of 10 to 30 mg, followed by 10 to 20 mg every 4 to 8 hours (maximum dosage: 180 mg daily)	[69]
Colorectal cancer	10 μM or 100 μM nifedipine for 24 h caused a significant decrease in proliferation rate	[70]
Migraine	Low dose of nifedipine 5 mg three times a day	[71]
Ureteral stones	20–30 mg per day	[72]
Achalasia	Nifedipine 10 mg sublingually 10–15 minutes premeal, relaxes LES by 30–40% for 60 minutes	[73]
Covid-19	30 mg extended release every 12 hours	[73]
Glaucoma	30-90 mg/d long-acting formulations one time a day	[74]
Chilblains	20–60 mg given three times daily	[75]

2. Advanced use of NIFE

2.1. Raynaud's phenomenon

Raynaud's phenomenon (RP) is a complex vasospastic disorder with multifactorial etiology, manifesting as transient, recurrent, and reversible constriction of peripheral blood vessels [76]. This occurs in tiny blood vessels supplying to extremities, especially when exposed to cold or stimulation by the sympathetic nervous system connective tissue diseases, e.g., systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome) such as during emotional stress [77]. RP can be classified as primary (with no associated cause - also known as Raynaud's disease, can run in families) or secondary (when concomitant with an underlying etiology, such as and is more common in women than men [78,79].

RP can induce significant digital pain and functional impairment, particularly among individuals with underlying connective tissue diseases [80]. The pathophysiology of RP is complex, but digital ischemia is a crucial factor [80]. Furthermore, the transient interruption of blood flow in RP is hypothesized to be modulated by neural and vascular mechanisms. Both structural and functional changes in blood vessels contribute to vascular abnormalities in RP [81]. However, functional impairment emerges as a primary determinant in the pathophysiology of primary Raynaud's phenomenon. Essential substances such as endothelin-1, angiotensin, and angiopoietin-2 play a substantial role in the vessel-mediated pathophysiology of RP. The role of nitric oxide in the manifestation of this phenomenon remains intricate [76,82]. Central or peripheral mechanisms recognise neural aberrations associated with RP [83]. Central nervous system (CNS) involvement in RP may be indicated by the notable triggers of an attack, such as emotional distress and low temperature [84,85]; however, recent studies highlight the significance of locally produced factors such as impaired vasodilation, heightened vasoconstriction, and various intravascular abnormalities that are identified as potential contributors to the onset of this disease [86,87]. Additionally, RP has been noted as an adverse effect of pharmaceutical agents [75].

2.1.1. Pharmacotherapy

Recent advancements in understanding the mechanisms involved in the pathophysiology of RP have led to developing more disease-specific pharmacological therapeutic approaches. However, primary management strategies for individuals afflicted by this disorder involve general lifestyle modifications and non-pharmacological interventions [88]. Pharmacotherapeutic modalities such as calcium channel blockers [89], alpha-1 adrenoreceptor antagonists, angiotensin-converting enzyme inhibitors [90], nitric oxide [91], prostaglandin analogs, and phosphodiesterase inhibitors have been identified as major drug classes with therapeutic significance in RP management. In addition to pharmaceutical interventions, non-pharmacological strategies, including anxiety management, avoidance of cold exposure, smoking cessation and other simple modifications, have demonstrated significant efficacy, particularly in individuals with milder symptoms [75].

2.2. Preterm labor

Preterm labor (PTL) is characterized by the occurrence of systematic uterine contractions concomitant with cervical alterations, specifically, cervical dilatation of ≥2 cm, initiated before the completion of 37 weeks of gestation [92]. Preterm birth, constituting 5 to 18% of pregnancies, stands as a prominent contributor to infant morbidity and mortality. The predominant etiology of preterm births, encompassing 70% of cases, is spontaneous preterm labor [93].

Inflammation is a specific pathogenic mechanism in preterm delivery [94]. However, birth canal infections are a significant factor exerting a substantial impact on perinatal morbidity and mortality [95]. Recent studies have focused on investigating further potential causes, notably disturbances in hormone metabolism or uteroplacental ischemia. This process is intricately linked to both maternal and fetal factors. The fetal inflammatory response (FIRS), which may manifest independently of the maternal response, correlates with a significant escalation in perinatal morbidity [96]. Secondary and tertiary prevention is crucial to screening high-risk women and

employing novel laboratory and ultrasound tests [97]. A thorough investigation of conceivable trigger mechanisms includes a variety of gene types that may be linked to the beginning of premature delivery [98].

2.2.1. Pharmacotherapy

The objective of therapeutic measures when premature labor is present is to prolong the time until birth by:

1) Inhibiting or reducing the frequency and intensity of contractions.

2) Optimizing fetal condition before premature delivery [99].

Pharmacological agents that can be used involve corticosteroids, ß-agonists, calcium channel blockers (such as NIFE) [100,101], magnesium sulfate administered for the management of PTL [102] and prostaglandin inhibitors, and nonsteroidal anti-inflammatory drugs (such as indomethacin) [66]. NIFE can also be used to stop preterm labor, which is when contractions begin before 37 weeks of pregnancy. It works by relaxing the muscles in the uterus, which can help delay delivery and give the baby more time to develop. By delaying the birth of the child, it also reduces morbidity and mortality associated with it [103]. The dose of NIFE used in PTL is indicated in Table 5.

2.3. Colorectal Cancer

Colorectal cancer (CRC) ranks second in cancer mortality and third in cancer morbidity worldwide, making it one of the most fatal diseases that costs millions of lives every year [104].

The L-type calcium channel is a subtype of voltage-gated calcium channels (VGCCs) responsible for regulating the influx of calcium ions in response to membrane depolarization [105]. VGCCs are primarily expressed in neurons, muscle cells, and neuroendocrine cells [106]. These channels can be categorized into high voltage-activated types (L-, N-, P/Q-, and R-types) and low voltage-activated types (T-type), all encoded by alpha one subunit genes known as CACNA1. Notably, evidence indicates elevated expression of L-type calcium channels in colorectal cancer (CRC) tissues compared to normal tissues [107].

2.3.1. Pharmacotherapy

The antitumor effects of NIFE have gained attention in recent years, with primary focus on drug resistance and inhibition of the proliferation and invasion of CRC cells [108]. NIFE inhibits calcium influx, weakens the activation of the nuclear factor of activated T cells (NFAT2) and impairs the dephosphorylation [109,110]. Furthermore, activation and nuclear translocation of NFAT2, which can be upregulated by LASP1, a protein closely related to the development and metastasis of CRC, prevents STAT3 recruitment and the transcriptional activation of downstream signalling molecules, inhibiting the proliferation and metastasis of cancer cells. Moreover, NIFE also acts on lymphocytes to reactivate tumor immunity, achieving comprehensive prevention and treatment of CRC based on the tumor itself and tumor immunity [111–113] as shown in Fig. 4.

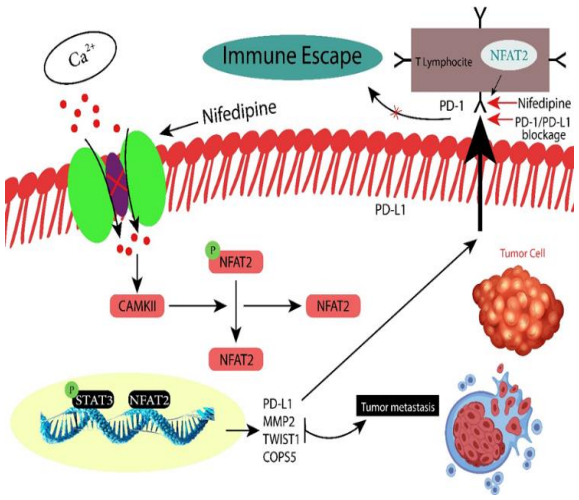

Fig. 4. This figure highlights the immunological escape that occurs through the disruptive effect of nifedipine. Furthermore, it highlights the process of the entry of calcium into cells, which ultimately inhibits cancer cells' proliferation and metastasis.

NIFE inhibits the expression of PD-L1 in tumor cells and the expression of PD-1 in T lymphocytes, thus mimicking the role of PD-1/PD-L1 inhibitors in tumors and promoting T lymphocytes' immune recognition of tumor cells, as shown in Figure 4. This demonstrates the importance of selecting appropriate antihypertensive drugs to treat cancer patients and provides a sufficient scientific basis for their use in CRC patients, especially in those with hypertension [114].

2.4. Migraine

Migraine is a persistent neurological disorder characterized by recurrent episodes of moderate to severe headache [115], accompanied by reversible neurological and systemic manifestations that mainly involve a heightened sensitivity to light (photophobia), sound (phonophobia), cutaneous allodynia, and gastrointestinal symptoms like nausea and vomiting. Furthermore, individuals may experience additional neurological symptoms, such as vertigo, dizziness, tinnitus, and cognitive impairment [116,117].

A painful, underdiagnosed, and undertreated condition, chronic migraine is defined as ≥ 15 headache days per month for ≥ three months, in which ≥ 8 days per month fulfills criteria for migraine with or without aura or responds to migraine-specific treatment [118,119]. In chronic migraine, the central nervous system, including the brain and its associated tissues, plays a pivotal role during episodes [120]. Initially regarded as a vascular disorder, now there is a paradigm shift, recognizing migraine as an intricately orchestrated interplay involving significant contributions from both peripheral and central nervous systems [121,122]. Key elements in this interaction involve the trigeminovascular system and the cerebral cortex. Advances in ***in vivo*** and ***in vitro*** methodologies have highlighted the relevance of phenomena such as cortical spreading depression and the activation of the trigeminovascular system, including its constituent neuropeptides. Furthermore, the significance of neuronal, glial ion channels and transporters was also observed, which contributes to a purported imbalance

between cortical excitatory and inhibitory processes, thereby rendering individuals susceptible to migraine attacks, significant disability, poor quality of life related to health, and a high financial burden [123].

2.4.1. Pharmacotherapy

A disease-specific treatment approach for migraine involves acute attack management for immediate relief and long-term preventive therapy to reduce attacks' frequency, severity, and duration [124]. Certain pathological conditions warranting preventive treatment include (a) Significant interference with daily routine despite acute treatment; (b) Issues with acute medication such as failure, contraindications, or troublesome side effects; (c) Overuse of acute medications; (d) Particular circumstances like hemiplegic migraine; (e) Persistent headaches (more than two a week); (f) Patient preference [125,126].

Preventive drug selection should consider proven efficacy, patient preferences, headache profile, drug side effects, and coexisting or comorbid diseases. High-efficacy drugs with mild to moderate adverse events include beta-blockers, amitriptyline, and divalproex. Drugs with lower efficacy and mild to moderate adverse events comprise selective serotonin reuptake inhibitors (SSRIs), gabapentin, topiramate, riboflavin, non-steroidal anti-inflammatory drugs, and calcium channel antagonists such as NIFE [127,128]. The effect produced by NIFE is shown in Fig. 5 Initiating the chosen drug at a low dose is advisable [129].

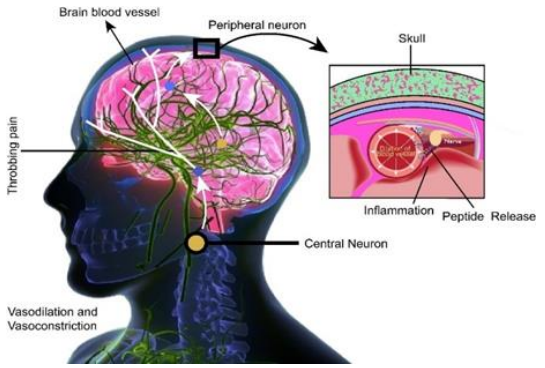

Fig. 5. A diagram examines the neurological and circulatory elements associated with the sensation of pulsating pain by providing a comprehensive representation of the human brain, particularly the complex structure of blood veins that play a crucial role in supplying essential oxygen and nutrients. A peripheral neuron located near an inflamed region is magnified in an inset picture, revealing its activity in response to painful stimuli. Central neurons, located deep inside the brain structure, play a crucial role in delivering pain signals.

The figure is augmented with text annotations that precisely identify each constituent, such as the cerebral blood arteries, peripheral and central neurons, and the skull. Additionally, the annotations emphasize significant physiological processes, such as the widening and narrowing of blood vessels, providing an understanding of the intricate cerebral networks implicated in the sensation of pulsating pain.

2.5. Ureteral Stones

Individuals having stones stuck in the ureter, the tube that carries urine from the kidney to the bladder, frequently experience pain and seek medical care [130]. Major symptoms involve pain in the flanks or abdomen that travels to the groin or external genitalia. However, some patients may not experience any symptoms; many do and, as a result, frequently seek medicinal therapy [130]. A stone present in the ureter causes the pressure in the pyelocalyceal system to increase periodically, which might result in an acute colic episode, although most of the stones have the characteristic of spontaneous passing [131].

2.5.1. Pharmacotherapy

NIFE is a proven pharmacological approach for managing urolithiasis, attributable to its spasmolytic effects on the ureter [132]. It can eliminate the rapid uncoordinated component of ureteral smooth-muscle contraction in animal and human ureters while leaving the slower peristaltic activity unaltered. Results of various studies have substantiated the promotion of enhanced stone passage in individuals undergoing NIFE treatment (30 mg/day slow release for 20–30 days), supplemented with steroids as an anti-edema agent (25 mg/day of methylprednisolone or 30 mg/day of deflazacort for ten days). Furthermore, it shows heightened stone-expulsion rates, abbreviated expulsion times, diminished analgesic requirements, and favorable tolerability and safety profiles possessed by NIFE [133,134]. Nevertheless, caution is advised when administering NIFE to individuals with cardiovascular disease due to the potential for serious side effects such as hypotension or palpitations [135].

2.6. Achalasia

Achalasia is an uncommon esophageal smooth muscle condition marked by missing or spastic contractions in the esophageal body and poor relaxation of the lower esophageal sphincter (LES) [136,137]. The primary pathophysiological process is the loss of inhibitory nerve function, primarily due to an autoimmune response that targets the myenteric nerves in the esophagus through mechanisms mediated by cells and potentially antibodies. Although achalasia can affect people of all ages and genders, its incidence and prevalence rise with age. Cardinal signs include dysphagia, regurgitation, chest discomfort, and weight loss [138,139].

2.6.1. Pharmacotherapy

A precise treatment plan is unavailable as the underlying cause of achalasia remains unknown [140]. Numerous oral pharmacological agents are employed in the therapeutic management of achalasia, encompassing calcium channel blockers (e.g., NIFE), long-acting nitrates (e.g., isosorbide dinitrate), phosphodiesterase-5 inhibitors (e.g., sildenafil), anticholinergics (e.g., atropine, dicyclomine), and beta-adrenergic agonists (e.g., terbutaline), with calcium channel blockers and long-acting nitrates emerging as the predominant choices. These agents promote oesophagal emptying by reducing smooth muscle tone and induction of smooth muscle relaxation within the lower oesophagal sphincter (LES) [137,141,142]. In cases where oral pharmacological

intervention is considered suitable, current recommendations involve administering NIFE sublingually at doses between 10 and 30 mg approximately 30 to 45 minutes before meals or isosorbide dinitrate at 5 mg 10 to 15 minutes before meals to achieve the best possible therapeutic efficacy [143].

2.7. Coronavirus disease (Covid-19)

COVID-19 is attributed to the recent pandemic virus that has cost millions of lives across the globe; it has another variant, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [144]. While vaccines are successfully developed, concurrent strategies in drug development play a crucial role in addressing SARS-CoV-2 and emerging viral threats [145]. Notably, coronaviruses rely on Ca^{2+} ions for host cell entry, and studies have highlighted the modulatory role of Ca^{2+} in the interaction between the viral fusion peptide and host cell membranes [146]. The efficacy of L-type calcium channel blocker (CCB) drugs in inhibiting SARS-CoV-2 infection in cell culture was investigated to expedite drug development. Various CCBs exhibited distinct levels of inhibition, with felodipine and NIFE demonstrating substantial efficacy in curtailing SARS-CoV-2 entry and infection in epithelial lung cells at concentrations where cellular toxicity remained minimal [147,148]. Subsequent investigations involving pseudo-typed particles displaying the SARS-CoV-2 spike protein suggested that the observed inhibition primarily occurs at the stage of virus entry. Collectively, these findings propose that specific CCBs such as NIFE hold promise as potential agents for treating SARS-CoV-2 infections, warranting further scrutiny of their possible role in COVID-19 treatment [149].

2.8. Glaucoma

Glaucoma, a chronic ocular ailment characterized by increased intraocular pressure (IOP), poses significant risks of ocular complications and potential vision impairment [150]. Pursuing effective treatments for such conditions has prompted the exploration of innovative pharmaceutical agents and drug delivery systems. The efficacy of NIFE in mitigating elevated IOP through vasodilatation in the smooth muscles of ocular blood vessels has been well established [151,152]. Utilizing NIFE-loaded in situ gels, a noteworthy reduction in IOP was observed without observable signs of ocular toxicity or irritation, offering a comparative assessment against conventional ophthalmic dosage forms [153].

2.9. Chilblains

Chilblains, called "perniosis," manifest as a localized skin inflammatory response induced by exposure to cold and damp conditions without reaching freezing temperatures [154,155]. It typically affects the fingers and toes but may also present on the nose and ears and tends to resolve spontaneously [156,157]. While the exact etiology remains uncertain, vasospasm is implicated in this aberrant response to cold. Diagnosis predominantly relies on clinical presentation, although a skin biopsy can be beneficial in cases posing diagnostic uncertainty [154].

CCB, such as NIFE, can effectively restrain the release of inflammatory factors, including TNF-α, IL-6, IL-1β, and VEGF. Moreover, it causes downregulation of mRNA levels of TRPC-6 and VEGF in the skin tissue. Furthermore, NIFE exerted inhibitory effects on the expression of IL-1β, IL-6, and TNF-α inflammatory proteins, along with concurrent suppression of TRP (transient receptor potential) family proteins, specifically TRPM-7, TRPC-1, TRPC-3, and TRPC-6. Additionally, a reduction in VEGF expression in the skin resulted in the alleviation of erythema and edema. This shows that NIFE holds potential as a novel therapeutic intervention for chilblains by modulating TRP family proteins and inflammatory mediators [158–161].

3. Conclusion

NIFE can effectively reduce blood pressure, induce vasodilation, and control angina and hypertension. However, it also shows potential in treating vasospastic disorders, urological problems, migraines, and colorectal cancer by regulating vascular function and preventing proliferation. In obstetrics, NIFE can improve fetal conditions and delay preterm labor. Emerging uses of NIFE include possible COVID-19 intervention, glaucoma, and achalasia. The adaptability of NIFE's pharmacological profile supports its broad usage for various medical conditions. However, further studies are necessary to realize its total therapeutic capacity, as it may potentially treat various life-threatening diseases, ultimately improving quality of life and reducing mortality.

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