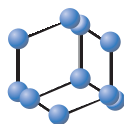


## REVIEW ARTICLE

BENTHAM  
SCIENCE

## Repurposing Cilostazol for Raynaud's Phenomenon



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**Abstract:** Raynaud's Phenomenon (RP) results from exaggerated cold-induced vasoconstriction. RP patients suffer from vasospastic attacks and compromised digital blood perfusion leading to a triple color change at the level the fingers. Severe RP may cause ulcers and threaten tissue viability. Many drugs have been used to alleviate the symptoms of RP. These include calcium-channel blockers, cGMP-specific phosphodiesterase type 5 inhibitors, prostacyclin analogs, and angiotensin receptor blockers. Despite their variety, these drugs do not treat RP but rather alleviate its symptoms. To date, no drug for RP has been yet approved by the U.S Food and Drugs Administration. Cilostazol is a selective inhibitor of phosphodiesterase-III, originally prescribed to treat intermittent claudication. Owing to its antiplatelet and vasodilating properties, cilostazol is being repurposed as a potential drug for RP. This review focuses on the different lines of action of cilostazol serving to enhance blood perfusion in RP patients.

**Keywords:** Cardiovascular disease, cilostazol, digital ischemia, drug repurposing, Raynaud's phenomenon, Cold-induced vasoconstriction.

## 1. INTRODUCTION

Reincarnation of old drugs to emerge as potential candidates for novel indication stems from the fact of promiscuity of drugs and their interaction with multiple molecular targets. This process has become a hallmark in the drug development strategy due to the high attrition rate of newly developed medicinal entities. Assigning a new task for an outdated or an already approved drug is also known as drug repurposing or repositioning.

A striking example is a case of acetylsalicylic acid, mentioned in the old Pharaonic medicinal papyrus, which recommended salicylic extracts as a painkiller to reduce fever [1]. Acetylsalicylic acid had to wait until the 19<sup>th</sup> century to be commercialized by Bayer as Aspirin. The popularity of Aspirin (acetylsalicylic acid)

grew faster in the 20<sup>th</sup> century with the discovery of its antiplatelet activity. Since then, Aspirin has become a frontline medicinal agent currently used all over the world in patients with increased risk of Cardiovascular Disease (CVD) [2]. As such, it is now established that the on or off-target effect of a drug is a proof-of-concept of polypharmacology, which is the ability of a therapeutic application to interfere with multiple disease pathways [3]. These effects are often discovered by serendipitous observations of post-marketing observations. Alternatively, drugs' effects may be inferred from wet laboratory experiments or during clinical studies. Thus, drug repurposing can revive a previously withdrawn drug.

A relevant example is the case of thalidomide, whose side effects impacted the pharmaceutical industry for years. Thalidomide showed teratogenic activities in fetuses worldwide and caused severe birth defects in pregnant women [4]. In fact, thalidomide was first prescribed for sleep disorders and morning sickness. Later, researchers accidentally discovered its anti-angiogenic and immunomodulatory properties, leading

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to the official approval of thalidomide as a treatment for leprosy and multiple myeloma [5, 6]. Furthermore, a repurposing success story is the case of sildenafil (Viagra<sup>®</sup>), a drug developed primarily for the treatment of pulmonary hypertension and coronary artery disease [7]. Unexpectedly, sildenafil treatment improved erectile function in the early phases of trials. This observed side effect through the inhibition of phosphodiesterase-5 (PDE-5) resulted in a novel indication of sildenafil, now a blockbuster drug prescribed for erectile dysfunction [8]. Another drug, minoxidil, a potassium channel opener and originally developed as an antihypertensive indication, is now successfully indicated in males with alopecia.

## 2. RAYNAUD'S PHENOMENON

A growing body of evidence supports the notion of drug repurposing in CVD, the leading cause of morbidity and mortality worldwide [9]. Particularly, the drug repurposing approach may be employed in the hunt for a more efficacious treatment for several cardiovascular diseases including Raynaud's Phenomenon (RP). RP is a CVD with no Food and Drug Administration (FDA)-approved drug [10, 11]. It is a pathological condition caused by exaggerated cold-induced vasoconstriction [12]. RP patients suffer from vasospastic attacks and triple color change (pallor, cyanosis, and erythema), primarily at the level of digits [13]. Based on the etiology of disease, clinicians classify RP into primary or secondary [14]. Primary RP occurs in the absence of any associated disease. By contrast, secondary RP is related to an underlying pathological condition or the use of certain drugs (Table 1) [13, 15-17]. In certain cases, such as in systemic sclerosis-related RP, patients can develop digital ulceration, scarring, or gangrene [12, 18, 19].

Evidence indicates that RP results from increased vascular sensitization to cold mediated by neuronal (norepinephrine) and local effectors [20, 21]. The latter are alpha adrenergic receptors ( $\alpha$ -ARs) on vascular smooth muscle cells (VSMCs) of cutaneous arterioles [20, 21]. These VSMCs express two types of  $\alpha$ -ARs:  $\alpha_1$ -ARs and  $\alpha_2$ -ARs. The inhibition of  $\alpha_1$ -ARs did not affect cold-induced vasoconstriction, ruling out the implication of these receptors in RP [22].

Alpha-2 ARs, on the other hand, are further subdivided into A, B, and C subtypes, with only A and C subtypes being expressed in human cutaneous VSMCs [23]. Notably, inhibiting  $\alpha_{2C}$ -ARs, but not  $\alpha_{2A}$ -ARs, abolished cold-induced vasoconstriction [22]. This

suggests that the entirety of cold-induced vasoconstriction is solely mediated via  $\alpha_{2C}$ -AR. In fact,  $\alpha_{2C}$ -AR is distinctively characterized by its intracellular localization [24]. We have previously shown that in response to certain stimuli, such as cold,  $\alpha_{2C}$ -ARs are translocated to the plasma membrane [25, 26]. We have also shown that the secondary messenger, cyclic AMP (cAMP), not only increases expression but also potentiates cell-surface localization of  $\alpha_{2C}$ -ARs in human arteriolar smooth muscle cells [27, 28]. This spatial mobilization functionally rescues  $\alpha_{2C}$ -ARs, allowing them to bind to their ligands thus provoking vasoconstriction [26].

Several traditional and nontraditional drugs or approaches have been used to alleviate the symptoms of RP (Table 2) [16]. These include calcium channel blockers, which are indeed the first line of treatment [29]. These agents act by preventing the calcium-induced contraction of VSMCs and subsequently alleviate vasoconstriction [30]. However, evidence of their efficacy is not overwhelming, and their use is associated with several adverse events [31, 32]. Indeed, two recent Cochrane reviews show that the use of CCBs for primary RP, although better than that for secondary RP, remains moderately effective in treating some aspects of the disease but ineffective in others [31, 32].

Other vasodilators have also been employed for the management of RP. These include inhibitors of the cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE5). These drugs, the most known of which is sildenafil, cause the accumulation of cGMP in VSMCs leading to their relaxation [33]. Interestingly, the efficacy of these drugs was similar to that of the widely used CCBs [34].

Other drugs that interfere with the angiotensin-II-induced vasoconstriction have also been utilized in the management of RP [33]. Indeed, angiotensin converting enzyme-I (ACE) inhibitors and angiotensin-II receptor blockers, which prevent the formation of angiotensin-II or block its receptor, respectively, have also been employed [33, 36]. In clinical trials, both classes of drugs show variable efficacy, with inconsistent reports regarding their therapeutic value in RP [16].

Activators or analogues of prostaglandin and prostacyclin have been documented to impart a therapeutic value owing to their antiplatelet and vasodilatory capacities. In specific, iloprost, which activates Prostaglandin E2 (PGE2) and Prostacyclin I2 (PGI2) receptors, shows promising potential as a treatment for severe non-responsive RP [33].

**Table 1. List of the most common diseases, conditions, and drugs responsible for the development of secondary RP [13, 16, 35].**

Category	Examples
Drug-induced	Beta-blockers, cisplatin, polyvinyl chloride, interferon-alpha, nicotine, cyclosporine, clonidine, bleomycin, methysergide, and cocaine.
Rheumatological disorders	Systemic sclerosis, vasculitis, systemic lupus erythematosus (SLE), Sjogren's syndrome, and idiopathic inflammatory myopathies.
Hematological disorders	Polycythemia, cryoglobulinemia (thickening of plasma due to presence of antibodies known as cryoglobulins), cryofibrinogenemia (the precipitation of fibrinogen and related products in the blood), paraproteinemia, and angiocentric lymphoma.
Structural disorders	Thoracic outlet syndrome, Takayasu's arteritis, Buerger's disease, carpal tunnel syndrome, and atherosclerosis.
Others	Endocrinological disorders (hypothyroidism), fibromyalgia, and prolonged manual vibration through use of Jackhammers.

**Table 2. The most commonly used pharmacological interventions for RP, their underlying mechanisms, indications for use, and associated adverse effects.**

Drug class	Mechanism of action	Indication/ Effectiveness in RP	Adverse effects	References
Calcium channel blockers (CCBs)	Block the influx of calcium into VSMCs and prevent their contraction	Orally administered as first line treatment/Effective	Hypotension, headaches, dizziness, tachycardia, facial and generalized edema	[30-32, 37]
PDE-5 inhibitors	Promote the accumulation of cGMP and enhance the relaxation of VSMCs	Orally administered if CCBs fail/ Similar effectiveness to CCBs	Headache, flushing, nausea, vomiting, facial and generalized edema	[33, 34, 37]
ACE inhibitors	Block the enzyme that converts angiotensin-I into the vasoactive angiotensin-II	-/Controversial effectiveness	Renal dysfunction, hyperkalemia, cough, hypotension	[16, 33, 36, 38]
Angiotensin-II receptor blockers	Inhibit the receptors that transduce the vasoconstrictive effects of angiotensin-II	May be orally administered to patients that do not tolerate CCBs/ Controversial effectiveness	Fatigue, dizziness, diarrhea, headache	[16, 33, 35-37]
Iloprost (PGE 2 and PGI2 agonist)	Precipitates antiplatelet and vasodilatory effects	IV administered in severe RP that does not respond to CCBs and PDE-5 inhibitors/Effective	Hypotension, rash, phlebitis, diarrhea, flushing, headache	[33, 37]

Besides these traditional pharmacological approaches, nontraditional ones that include Botulinum toxin type A injection, laser treatment, and acupuncture have also been employed [16]. Moreover, several lifestyle changes are recommended to reduce the frequency of attacks. These changes include keeping the extremities warm, smoking cessation, refraining from the consumption of certain medications, and avoiding emotional stressors [37].

Despite the variability of the aforementioned approaches/drugs, none has been used as a definitive RP

treatment. Contextually, to date, no specific drug has been yet approved by the U.S. FDA to treat RP [11]. This may be due to several challenges. First, the multi-etiology of the disease (local, neuronal, and hormonal basis) hinders a complete, or at least a sufficient, understanding of RP pathophysiology, thus presenting a real challenge in designing the appropriate treatment [11, 39]. Furthermore,  $\alpha_{2C}$ -AR, the key player in mediating RP, is expressed in many brain regions and is implicated in the presynaptic regulation of the heart. Therefore, drugs targeting  $\alpha_{2C}$ -AR will likely interfere

with brain and heart functions, causing deleterious side effects [16]. In addition, the absence of an animal model for RP further increases the level of the challenge [16]. Given these limitations, drug repurposing appears as a window of opportunity in the realm of RP treatment.

### 3. CILOSTAZOL REPURPOSED

Cilostazol (PubChem ID: 2754), a quinolinone derivative, is a drug known for its vasodilatory and antiplatelet effects [40]. These effects are attributed to the drug's function as a reversible inhibitor of the cyclic adenosine monophosphate (cAMP) phosphodiesterase III (PDE-3) [40]. Cilostazol was first approved by the FDA in 1999 to treat intermittent claudication (IC), a condition of calf muscle pain prevalent in patients with the peripheral arterial disease (PAD). Currently, this drug is available in two formulations 50 mg and 100 mg oral tablets [41].

Several clinical studies have been conducted to evaluate the efficiency of cilostazol in alleviating IC symptoms. A meta-analysis reported that cilostazol significantly increased maximal walking distance and pain-free walking distance by 50% and 67% respectively [42]. In addition, a recent Cochrane review reinforced this cilostazol-enhanced walking distance in IC patients [43]. The documented improvement is attributed to the role of cilostazol in granting adequate blood supply to the lower extremities of the body [44].

Furthermore, cilostazol is adopted in Japan as part of secondary prevention of cerebral infarction plans and stroke management guidelines [45]. This use is backed-up by extensive evidence on the effectiveness and safety of cilostazol in the aforementioned situations. In fact, a large randomized controlled trial showed that cilostazol is slightly more effective than Aspirin in stroke prevention and elicited greater safety than the latter concerning risk of hemorrhage [45]. These findings were further reinforced by a metanalysis of similar clinical trials [46]. This cilostazol-induced enhancement of blood perfusion in different pathologies prompted further investigation on the possibility of using the drug to treat other blood flow conditions. Indeed, studies have proven the efficiency of cilostazol in prophylaxis against symptomatic intracranial arterial stenosis [47] and in ameliorating ischemia-induced injury [48]. As such, cilostazol may present a potential drug for vascular insufficiency conditions, such as RP.

Evidence shows that cilostazol opposed vasospastic contractions in RP patients [40]. Due to its PDE-3 in-

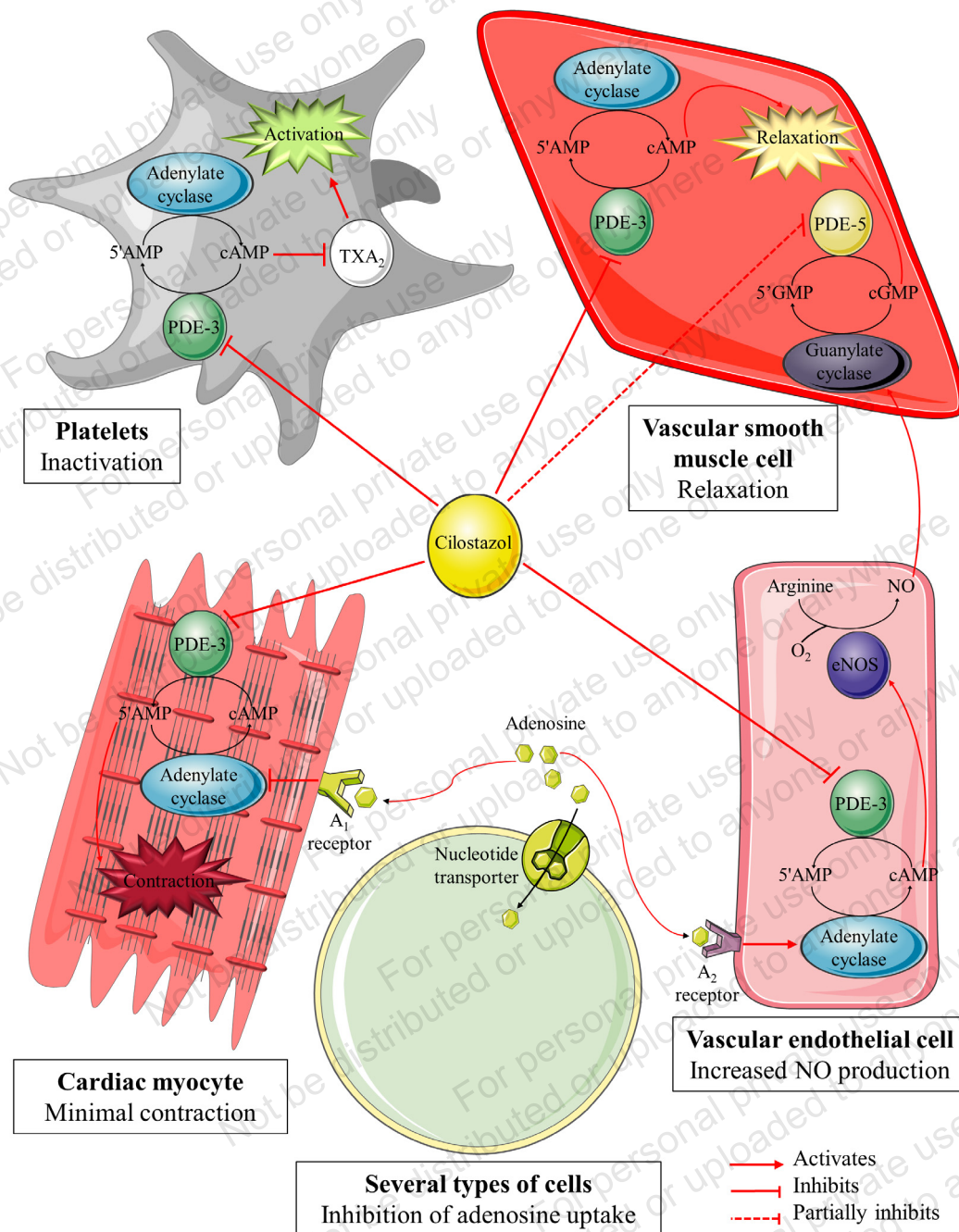
hibitory function, cilostazol resulted in the accumulation of cAMP, thus inducing vasodilation (Fig. 1) [40]. This cAMP-mediated vasorelaxant effect is elicited mainly via two distinct pathways. One relies on the cAMP-dependent secretion of nitrogen oxide (NO) by vascular endothelial cells [49]. The other signaling pathway is endothelium-independent and involves the direct effect of cilostazol on VSMCs. In fact, cyclic-AMP build-up in these cells induces PKA-dependent activation of the calcium-dependent potassium channel (BKCa), ultimately leading to vasorelaxation [50]. Additional mechanisms underlying the vasodilatory effects of the cilostazol have been recently highlighted. For instance, cilostazol was shown to inhibit another phosphodiesterase, namely the cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase or phosphodiesterase V (PDE-5) [51]. This inhibition, although mild, can contribute to the vasorelaxant properties by promoting the accumulation of cGMP in VSMCs [51]. Furthermore, cilostazol attenuates adenosine uptake by several cell types, thereby leading to adenosine build-up in the interstitial fluid and vascular circulation (Fig. 1) [52]. It is this increase in extracellular adenosine that potentiates adenosine receptor A2 activity in endothelial cells, eventually causing arterial dilatation [53]. It is worth mentioning that the concentrations of cilostazol needed to inhibit adenosine uptake or to block PDE-3 are very similar [51].

Modulation of platelet activity is another route by which cilostazol favorably alleviates symptoms of RP. It has been reported that platelet hyperactivity is associated with reduced perfusion in both primary RP and that secondary to systemic sclerosis [54]. Contextually, cilostazol significantly lowered the number of activated platelets as well as decreased the concentrations of soluble adhesion molecules and platelet microparticles (PMPs) [55]. This effect is mediated via cAMP-dependent inactivation of thromboxane A2 (TXA<sub>2</sub>) inside the platelets, thus preventing their activation [56].

Cilostazol presents several characteristics making it selectively more attractive than other PDE-3 inhibitors, at least in the context of RP. Indeed, when compared to milrinone, another PDE3 inhibitor, cilostazol, was found to have a more pronounced effect on platelets and vascular cells [57]. In addition, cilostazol spares cardiac myocytes from cAMP-induced positive inotropic effects that are otherwise prevalent with other PDE-3 inhibitors (Fig. 1) [57]. These diminished inotropic effects are linked to the cilostazol-induced accumulation of adenosine, which can activate A1 adenosine receptors present on cardiac myocytes [51].

These A1 receptors, along with their associated inhibitory G protein ( $G_i$ ) can counteract the cAMP elevation induced by PDE-3 inhibition [51, 53]. Thus, this decreased cardiac side effect of cilostazol is especially appealing in the context of RP treatment due to the al-

ready established associations between RP and dangerous cardiac events such as angina [58]. The various signaling mechanisms initiated or inhibited by cilostazol are illustrated in Fig. (1).



**Fig. (1). Mechanisms of action of cilostazol.**

Cilostazol activates or inhibits several pathways in various cell types to induce vasodilatation and enhance blood perfusion. Cilostazol induces NO release by endothelial cells and activates calcium-dependent potassium channels in VSMCs, leading to vasodilatation. In addition, cilostazol leads to adenosine build up in interstitial fluid consequently activating adenosine receptor A<sub>2</sub> in endothelial cells, and eventually causing arterial dilatation. Furthermore, cilostazol attenuates the activation of platelets and lowers PMPs concentration, thus facilitating blood perfusion. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Clinical trials testing the efficacy and the applicability of the future use of cilostazol to treat RP are limited; however, they seem to be encouraging. Indeed, in a randomized trial, 30 subjects (19 patients with primary RP and 21 patients with secondary RP) received 100 mg cilostazol or placebo twice daily for 6 weeks, after which several parameters related to vascular circulation were measured [59]. A significant increase in the diameter of the brachial artery was described; however, no associations with flow mediated dilation (FMD) or with the frequency and severity of vasospastic attacks were reported [59]. The strength of this trial lies in the use of a placebo group and the conduction of the trial over two winter seasons to account for any possible confounding variations between the seasons. A drawback of this study is that the frequency and severity of attacks before starting the trial were not reported, especially that these parameters may be used as an important reference to evaluate the progress. Another clinical trial included 21 patients presented with RP secondary to systemic sclerosis [60]. They all received 100 mg of cilostazol twice daily for 12 months, and different parameters pertaining to the vasculopathy of RP were measured pre- and post-treatment [60]. This study showed a statistically significant increase in the brachial artery diameter with a  $36\% \pm 11\%$  drop in the total number of attacks and a  $46\% \pm 12\%$  drop in their mean duration [60]. Although this study compares the parameters before and after treatment and tests the statistical significance of observed changes, the absence of a control group that can totally rule out the spontaneous resolution of symptoms presents a major limitation of the study. That said, these studies provide the justification for the increased attention to cilostazol as a potential drug being repurposed for RP.

On the other hand, several studies conducted on cilostazol, whether RP-related or not, suggest that the drug can precipitate a number of adverse events. The most common side effect is headache, affecting 35% of the patients receiving cilostazol versus zero in the control group [48]. This sequel, which is attributed to the vasodilatory action of cilostazol, can be alleviated by decreasing the initial dose of the drug or by increasing the dosage rate [61]. Another commonly reported undesired reaction is palpitations, which in turn are attributed to the previously mentioned inotropic effect of the drug [61]. Importantly, the company that produced the initial patented product, Pletal, warned that these palpitations can lead to angina pectoris in patients at risk [62]. The addition of beta blockers to the treatment regimens of these patients is recommended [61].

A third reported event is epistaxis, which is anticipated to be a result of cilostazol's antiplatelet capacity [45]. Other occasionally reported adverse events of cilostazol include diarrhea, vomiting, and bloating [48, 49]. Finally, although the drug does not show significant cardiovascular events in normal subjects, its use is contraindicated in patients with congestive heart failure. This contraindication is inspired by the increased mortality risk posed by similarly-acting drugs on patients with advanced-level heart failure [61]. Other contraindications include pregnancy and peptic ulcer disease or other pathologies that predispose patients to bleeding [62]. Being a PDE inhibitor, cilostazol should not be used with topical nitrates at the same time [63]. This precaution is especially important to avoid hypotension, peripheral edema, and other serious auditory and visual complications [63]. Therefore, cilostazol, just like any other medication, has certain adverse effects and contraindications that need to be taken into consideration when prescribing the drug in a clinical setting.

## CONCLUSION

In summary, current RP treatments are still insufficient, and preventive measures are by far the most effective way to reduce RP symptoms. Interestingly, cilostazol appears to be a promising treatment in the war against RP. However, conclusive well-structured trials with a large sample size are warranted to validate the efficacy of cilostazol in this context. As such, further investigation and research in this domain are of utmost importance. In addition, the cooperative and collaborative efforts of researchers and clinicians must be enhanced to document and analyze the emerging results. This is important, especially that a 20-year analysis showed that RP is associated with a 1.6-fold increase in CVD-related morbidity [58], suggesting that RP may present a sign of pre-clinical cardiovascular disease [13, 58].

## LIST OF ABBREVIATIONS

ACE	=	Angiotensin Converting Enzyme
AMP	=	Adenosine Monophosphate
AR	=	Adrenergic Receptor
BKCa	=	Calcium-dependent Potassium Channel
cAMP	=	Cyclic Adenosine Monophosphate
CCB	=	Calcium Channel Blocker
cGMP	=	Cyclic Guanosine Monophosphate
CVD	=	Cardiovascular Disease

FDA = Food and Drug Administration  
 FMD = Flow Mediated Dilation  
 GMP = Guanosine Monophosphate  
 IC = Intermittent Claudication  
 NO = Nitric Oxide  
 PAD = Peripheral Arterial Disease  
 PDE = Phosphodiesterase  
 PGE2 = Prostaglandin E2  
 PGI2 = Prostacyclin I2  
 PKA = Protein Kinase A  
 PMP = Platelet Microparticles  
 RP = Raynaud's Phenomenon  
 SLE = Systemic Lupus Erythromatosus  
 TXA<sub>2</sub> = Thromboxane A2  
 VSMC = Vascular Smooth Muscle Cell

#### CONSENT FOR PUBLICATION

Not applicable.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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#### REFERENCES

- [1] Vane, J.R. The fight against rheumatism: from willow bark to COX-1 sparing drugs. *J. Physiol. Pharmacol.*, **2000**, *51*(4 Pt 1), 573-586. PMID: 11192932
- [2] Desborough, M.J.R.; Keeling, D.M. The aspirin story - from willow to wonder drug. *Br. J. Haematol.*, **2017**, *177*(5), 674-683. <http://dx.doi.org/10.1111/bjh.14520> PMID: 28106908
- [3] Flemming, A. Cancer: Of targets and anti-targets. *Nat. Rev. Drug Discov.*, **2012**, *11*(7), 515. <http://dx.doi.org/10.1038/nrd3781> PMID: 22722534
- [4] Jourdan, J.P.; Bureau, R.; Rochais, C.; Dallemagne, P. Drug repositioning: a brief overview. *J. Pharm. Pharmacol.*, **2020**. <http://dx.doi.org/10.1111/jphp.13273> PMID: 32301512
- [5] Holstein, S.A.; McCarthy, P.L. Immunomodulatory drugs in multiple myeloma: mechanisms of action and clinical experience. *Drugs*, **2017**, *77*(5), 505-520. <http://dx.doi.org/10.1007/s40265-017-0689-1> PMID: 28205024
- [6] Kale, V.P.; Habib, H.; Chitren, R.; Patel, M.; Pramanik, K.C.; Jonnalagadda, S.C.; Challagundla, K.; Pandey, M.K. Old drugs, new uses: drug repurposing in hematological malignancies. *Semin. Cancer Biol.*, **2020**, *68*, 242-248. <http://dx.doi.org/10.1016/j.semcancer.2020.03.005> PMID: 32151704
- [7] Goldstein, I.; Burnett, A.L.; Rosen, R.C.; Park, P.W.; Stecher, V.J. The serendipitous story of sildenafil: an unexpected oral therapy for erectile dysfunction. *Sex. Med. Rev.*, **2019**, *7*(1), 115-128. <http://dx.doi.org/10.1016/j.sxmr.2018.06.005> PMID: 30301707
- [8] Kass, D.A.; Champion, H.C.; Beavo, J.A. Phosphodiesterase type 5: expanding roles in cardiovascular regulation. *Circ. Res.*, **2007**, *101*(11), 1084-1095. <http://dx.doi.org/10.1161/CIRCRESAHA.107.162511> PMID: 18040025
- [9] Gelosa, P.; Castiglioni, L.; Camera, M.; Sironi, L. Drug repurposing in cardiovascular diseases: Opportunity or hopeless dream? *Biochem. Pharmacol.*, **2020**, *177*, 113894. <http://dx.doi.org/10.1016/j.bcp.2020.113894> PMID: 32142728
- [10] Dudley, J.; Berliocchi, L. *Drug repositioning: approaches and applications for neurotherapeutics*; CRC press, Boca Raton, vol. 1, **2017**. <http://dx.doi.org/10.4324/9781315373669>
- [11] Landry, G.J. Current medical and surgical management of Raynaud's syndrome. *J. Vasc. Surg.*, **2013**, *57*(6), 1710-1716. <http://dx.doi.org/10.1016/j.jvs.2013.03.012> PMID: 23618525
- [12] Herrick, A.L. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. *Nat. Rev. Rheumatol.*, **2012**, *8*(8), 469-479. <http://dx.doi.org/10.1038/nrrheum.2012.96> PMID: 22782008
- [13] Pauling, J.D.; Hughes, M.; Pope, J.E. Raynaud's phenomenon-an update on diagnosis, classification and management. *Clin. Rheumatol.*, **2019**, *38*(12), 3317-3330. <http://dx.doi.org/10.1007/s10067-019-04745-5> PMID: 31420815
- [14] Block, J.A.; Sequeira, W. Raynaud's phenomenon. *Lancet*, **2001**, *357*(9273), 2042-2048. [http://dx.doi.org/10.1016/S0140-6736\(00\)05118-7](http://dx.doi.org/10.1016/S0140-6736(00)05118-7) PMID: 11438158
- [15] Prete, M.; Fatone, M.C.; Favoino, E.; Perosa, F. Raynaud's phenomenon: from molecular pathogenesis to therapy. *Autoimmun. Rev.*, **2014**, *13*(6), 655-667. <http://dx.doi.org/10.1016/j.autrev.2013.12.001> PMID: 24418302
- [16] Fardoun, M.M.; Nassif, J.; Issa, K.; Baydoun, E.; Eid, A.H. Raynaud's phenomenon: a brief review of the underlying mechanisms. *Front. Pharmacol.*, **2016**, *7*, 438. <http://dx.doi.org/10.3389/fphar.2016.00438> PMID: 27899893
- [17] Lis-Święty, A. Recent advances in the workup and management of Raynaud phenomenon *Pol. Arch. Intern. Med.*, **2019**, *129*(11), 798-808. <https://doi.org/10.20452/pamw.15008> PMID: 31577265
- [18] Bakst, R.; Merola, J.F.; Franks, A.G., Jr; Sanchez, M. Raynaud's phenomenon: pathogenesis and management. *J. Am. Acad. Dermatol.*, **2008**, *59*(4), 633-653. <http://dx.doi.org/10.1016/j.jaad.2008.06.004> PMID: 18656283
- [19] Sama, C-B. Post-traumatic digital gangrene associated with epinephrine use in primary Raynaud's phenomenon: lesson for the future. *Ethiop. J. Health Sci.*, **2016**, *26*(4), 401-404.

- <http://dx.doi.org/10.4314/ejhs.v26i4.13> PMID: 27587939
- [20] Charkoudian, N. Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. *J. Appl. Physiol.*, **2010**, *109*(4), 1221-1228. <http://dx.doi.org/10.1152/jappphysiol.00298.2010> PMID: 20448028
- [21] Wigley, F.M.; Flavahan, N.A. Raynaud's Phenomenon. *N. Engl. J. Med.*, **2016**, *375*(6), 556-565. <http://dx.doi.org/10.1056/NEJMra1507638> PMID: 27509103
- [22] Chotani, M.A.; Flavahan, S.; Mitra, S.; Daunt, D.; Flavahan, N.A. Silent alpha(2C)-adrenergic receptors enable cold-induced vasoconstriction in cutaneous arteries. *Am. J. Physiol. Heart Circ. Physiol.*, **2000**, *278*(4), H1075-H1083. <http://dx.doi.org/10.1152/ajpheart.2000.278.4.H1075> PMID: 10749700
- [23] MacDonald, E.; Kobilka, B.K.; Scheinin, M. Gene targeting--homing in on  $\alpha$  2-adrenoceptor-subtype function. *Trends Pharmacol. Sci.*, **1997**, *18*(6), 211-219. [http://dx.doi.org/10.1016/S0165-6147\(97\)01063-8](http://dx.doi.org/10.1016/S0165-6147(97)01063-8) PMID: 9227000
- [24] von Zastrow, M.; Kobilka, B.K. Antagonist-dependent and -independent steps in the mechanism of adrenergic receptor internalization. *J. Biol. Chem.*, **1994**, *269*(28), 18448-18452. PMID: 7518433
- [25] Bailey, S.R.; Eid, A.H.; Mitra, S.; Flavahan, S.; Flavahan, N.A. Rho kinase mediates cold-induced constriction of cutaneous arteries: role of  $\alpha_{2C}$ -adrenoceptor translocation. *Circ. Res.*, **2004**, *94*(10), 1367-1374. <http://dx.doi.org/10.1161/01.RES.0000128407.45014.58> PMID: 15087420
- [26] Jeyaraj, S.C.; Chotani, M.A.; Mitra, S.; Gregg, H.E.; Flavahan, N.A.; Morrison, K.J. Cooling evokes redistribution of  $\alpha_{2C}$ -adrenoceptors from golgi to plasma membrane in transfected human embryonic kidney 293 cells. *Mol. Pharmacol.*, **2001**, *60*(6), 1195-1200. <http://dx.doi.org/10.1124/mol.60.6.1195> PMID: 11723226
- [27] Jeyaraj, S.C.; Unger, N.T.; Eid, A.H.; Mitra, S.; Paul El-Dahdah, N.; Quilliam, L.A.; Flavahan, N.A.; Chotani, M.A. Cyclic AMP-Rap1A signaling activates RhoA to induce  $\alpha(2c)$ -adrenoceptor translocation to the cell surface of microvascular smooth muscle cells. *Am. J. Physiol. Cell Physiol.*, **2012**, *303*(5), C499-C511. <http://dx.doi.org/10.1152/ajpcell.00461.2011> PMID: 22621783
- [28] Eid, A.H.; Chotani, M.A.; Mitra, S.; Miller, T.J.; Flavahan, N.A. Cyclic AMP acts through Rap1 and JNK signaling to increase expression of cutaneous smooth muscle alpha(2C)-adrenoceptors. *Am. J. Physiol. Heart Circ. Physiol.*, **2008**, *295*(1), H266-H272. <http://dx.doi.org/10.1152/ajpheart.00084.2008> PMID: 18487435
- [29] Halawa, B. Calcium channel blockers in the treatment of cardiovascular disease. *Pol. Merkur. Lekarski.*, **2001**, *11*(61), 83-87. PMID: 11579840
- [30] Sturgill, M.G.; Seibold, J.R. Rational use of calcium-channel antagonists in Raynaud's phenomenon. *Curr. Opin. Rheumatol.*, **1998**, *10*(6), 584-588. <http://dx.doi.org/10.1097/00002281-199811000-00013> PMID: 9812220
- [31] Rirash, F.; Tingey, P.C.; Harding, S.E.; Maxwell, L.J.; Tanjong Ghogomu, E.; Wells, G.A.; Tugwell, P.; Pope, J. Calcium channel blockers for primary and secondary Raynaud's phenomenon. *Cochrane Database Syst. Rev.*, **2017**, *12*CD000467 <http://dx.doi.org/10.1002/14651858.CD000467.pub2> PMID: 29237099
- [32] Ennis, H.; Hughes, M.; Anderson, M.E.; Wilkinson, J.; Herrick, A.L. Calcium channel blockers for primary Raynaud's phenomenon. *Cochrane Database Syst. Rev.*, **2016**, *2*CD002069 <http://dx.doi.org/10.1002/14651858.CD002069.pub5> PMID: 26914257
- [33] Negrini, S.; Magnani, O.; Matucci-Cerinic, M.; Carignola, R.; Data, V.; Montabone, E.; Santaniello, A.; Adorni, G.; Murdaca, G.; Puppo, F.; Indiveri, F.; Della Rossa, A.; D'Ascanio, A.; Barsotti, S.; Giuggioli, D.; Ferri, C.; Lumetti, F.; Bosello, S.L.; Canestrari, G.; Bellando Randone, S.; Bruni, C.; Guiducci, S.; Battaglia, E.; De Andres, M.I.; Russo, A.A.; Beretta, L. Iloprost use and medical management of systemic sclerosis-related vasculopathy in Italian tertiary referral centers: results from the PROSIT study. *Clin. Exp. Med.*, **2019**, *19*(3), 357-366. <http://dx.doi.org/10.1007/s10238-019-00553-y> PMID: 30989453
- [34] Lee, E.Y.; Park, J.K.; Lee, W.; Kim, Y.K.; Park, C.S.; Giles, J.T.; Park, J.W.; Shin, K.; Lee, J.S.; Song, Y.W.; Lee, E.B. Head-to-head comparison of udenafil vs amlodipine in the treatment of secondary Raynaud's phenomenon: a double-blind, randomized, cross-over study. *Rheumatology (Oxford)*, **2014**, *53*(4), 658-664. <http://dx.doi.org/10.1093/rheumatology/ket417> PMID: 24352340
- [35] Temprano, K.K. A review of raynaud's disease. *Mo. Med.*, **2016**, *113*(2), 123-126. PMID: 27311222
- [36] Regulska, M.; Regulska, K.; Staniszc, B.J.; Murias, M.; Gieremek, P.; Wzgarda, A.; Niznik, B. Chemistry and pharmacology of angiotensin-converting enzyme inhibitors. *Curr. Pharm. Des.*, **2015**, *21*(13), 1764-1775. <http://dx.doi.org/10.2174/1381612820666141112160013> PMID: 25388457
- [37] Linnemann, B.; Erbe, M. Raynaud's phenomenon and digital ischaemia--pharmacologic approach and alternative treatment options. *Vasa*, **2016**, *45*(3), 201-212. <http://dx.doi.org/10.1024/0301-1526/a000526> PMID: 27129065
- [38] Agustí, A.; Bonet, S.; Arnau, J.M.; Vidal, X.; Laporte, J.R. Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction : meta-analysis of randomised clinical trials. *Drug Saf.*, **2003**, *26*(12), 895-908. <http://dx.doi.org/10.2165/00002018-200326120-00004> PMID: 12959631
- [39] Wigley, F.M. Clinical practice. Raynaud's phenomenon. *N. Engl. J. Med.*, **2002**, *347*(13), 1001-1008. <http://dx.doi.org/10.1056/NEJMcp013013> PMID: 12324557
- [40] Dindyal, S.; Kyriakides, C. A review of cilostazol, a phosphodiesterase inhibitor, and its role in preventing both coronary and peripheral arterial restenosis following endovascular therapy. *Recent Pat. Cardiovasc. Drug Discov.*, **2009**, *4*(1), 6-14. <http://dx.doi.org/10.2174/157489009787260025> PMID: 19149700
- [41] Orange book: approved drug products with therapeutic equivalence evaluations. Available at: [https://www.accessdata.fda.gov/scripts/cder/ob/search\\_product.cfm](https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm) (accessed on: 24 March, 2021)
- [42] Cariski, A.T. Cilostazol: a novel treatment option in intermittent claudication. *Int. J. Clin. Pract. Suppl.*, **2001**, (119), 11-18. PMID: 11355274
- [43] Bedenis, R.; Stewart, M.; Cleanthis, M.; Robless, P.; Mikhailidis, D.P.; Stansby, G. Cilostazol for intermittent claudication. *Cochrane Database Syst. Rev.*, **2014**, *2014*(10), CD003748.

- <https://doi.org/10.1002/14651858.cd003748.pub4> PMID: 25358850
- [44] Yentes, J.M.; Huisinga, J.M.; Myers, S.A.; Pipinos, I.I.; Johanning, J.M.; Stergiou, N. Pharmacological treatment of intermittent claudication does not have a significant effect on gait impairments during claudication pain. *J. Appl. Biomech.*, **2012**, *28*(2), 184-191.  
<http://dx.doi.org/10.1123/jab.28.2.184> PMID: 22723116
- [45] Shinohara, Y.; Katayama, Y.; Uchiyama, S.; Yamaguchi, T.; Handa, S.; Matsuoka, K.; Ohashi, Y.; Tanahashi, N.; Yamamoto, H.; Genka, C.; Kitagawa, Y.; Kusuoka, H.; Nishimaru, K.; Tsushima, M.; Koretsune, Y.; Sawada, T.; Hamada, C. CSPS 2 group. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol.*, **2010**, *9*(10), 959-968.  
[http://dx.doi.org/10.1016/S1474-4422\(10\)70198-8](http://dx.doi.org/10.1016/S1474-4422(10)70198-8) PMID: 20833591
- [46] Kim, S.M.; Jung, J.M.; Kim, B.J.; Lee, J.S.; Kwon, S.U. Cilostazol mono and combination treatments in ischemic stroke: an updated systematic review and meta-analysis. *Stroke*, **2019**, *50*(12), 3503-3511.  
<http://dx.doi.org/10.1161/STROKEAHA.119.026655> PMID: 31607242
- [47] Kwon, S.U.; Cho, Y.J.; Koo, J.S.; Bae, H.J.; Lee, Y.S.; Hong, K.S.; Lee, J.H.; Kim, J.S. Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis: the multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. *Stroke*, **2005**, *36*(4), 782-786.  
<http://dx.doi.org/10.1161/01.STR.0000157667.06542.b7> PMID: 15746463
- [48] Nazli, Y.; Colak, N.; Namuslu, M.; Erdamar, H.; Haltas, H.; Alpay, M.F.; Nuri Aksoy, O.; Olgun Akkaya, I.; Cakir, O. Cilostazol attenuates spinal cord ischemia-reperfusion injury in rabbits. *J. Cardiothorac. Vasc. Anesth.*, **2015**, *29*(2), 351-359.  
<http://dx.doi.org/10.1053/j.jvca.2014.06.028> PMID: 25440635
- [49] Nakamura, T.; Houchi, H.; Minami, A.; Sakamoto, S.; Tsuchiya, K.; Niwa, Y.; Minakuchi, K.; Nakaya, Y. Endothelium-dependent relaxation by cilostazol, a phosphodiesterase III inhibitor, on rat thoracic aorta. *Life Sci.*, **2001**, *69*(15), 1709-1715.  
[http://dx.doi.org/10.1016/S0024-3205\(01\)01258-9](http://dx.doi.org/10.1016/S0024-3205(01)01258-9) PMID: 11665832
- [50] Li, H.; Hong, D.H.; Son, Y.K.; Na, S.H.; Jung, W.K.; Bae, Y.M.; Seo, E.Y.; Kim, S.J.; Choi, I.W.; Park, W.S. Cilostazol induces vasodilation through the activation of Ca<sup>2+</sup>-activated K<sup>+</sup> channels in aortic smooth muscle. *Vascul. Pharmacol.*, **2015**, *70*, 15-22.  
<http://dx.doi.org/10.1016/j.vph.2015.01.002> PMID: 25748552
- [51] Liu, Y.; Shakur, Y.; Yoshitake, M.; Kambayashi Ji, J. Cilostazol (pletal): a dual inhibitor of cyclic nucleotide phosphodiesterase type 3 and adenosine uptake. *Cardiovasc. Drug Rev.*, **2001**, *19*(4), 369-386.  
<http://dx.doi.org/10.1111/j.1527-3466.2001.tb00076.x> PMID: 11830753
- [52] Liu, Y.; Fong, M.; Cone, J.; Wang, S.; Yoshitake, M.; Kambayashi, J. Inhibition of adenosine uptake and augmentation of ischemia-induced increase of interstitial adenosine by cilostazol, an agent to treat intermittent claudication. *J. Cardiovasc. Pharmacol.*, **2000**, *36*(3), 351-360.  
<http://dx.doi.org/10.1097/00005344-200009000-00011> PMID: 10975593
- [53] Shryock, J.C.; Belardinelli, L. Adenosine and adenosine receptors in the cardiovascular system: biochemistry, physiology, and pharmacology. *Am. J. Cardiol.*, **1997**, *79*(12A), 2-10.  
[http://dx.doi.org/10.1016/S0002-9149\(97\)00256-7](http://dx.doi.org/10.1016/S0002-9149(97)00256-7) PMID: 9223356
- [54] Lau, C.S.; McLaren, M.; Saniabadi, A.; Belch, J.J. Increased whole blood platelet aggregation in patients with Raynaud's phenomenon with or without systemic sclerosis. *Scand. J. Rheumatol.*, **1993**, *22*(3), 97-101.  
<http://dx.doi.org/10.3109/03009749309099251> PMID: 8316776
- [55] Nomura, S.; Shouzu, A.; Omoto, S.; Hayakawa, T.; Kagawa, H.; Nishikawa, M.; Inada, M.; Fujimura, Y.; Ikeda, Y.; Fukuhara, S. Effect of cilostazol on soluble adhesion molecules and platelet-derived microparticles in patients with diabetes. *Thromb. Haemost.*, **1998**, *80*(3), 388-392. PMID: 9759615
- [56] Weintraub, W.S. The vascular effects of cilostazol. *Can J. Cardiol.*, **2006**, *22*(Suppl. B), 56B-60B.  
[http://dx.doi.org/10.1016/S0828-282X\(06\)70987-4](http://dx.doi.org/10.1016/S0828-282X(06)70987-4) PMID: 16498513
- [57] Cone, J.; Wang, S.; Tandon, N.; Fong, M.; Sun, B.; Sakurai, K.; Yoshitake, M.; Kambayashi, J.; Liu, Y. Comparison of the effects of cilostazol and milrinone on intracellular cAMP levels and cellular function in platelets and cardiac cells. *J. Cardiovasc. Pharmacol.*, **1999**, *34*(4), 497-504.  
<http://dx.doi.org/10.1097/00005344-199910000-00004> PMID: 10511123
- [58] Nietert, P.J.; Shaftman, S.R.; Silver, R.M.; Wolf, B.J.; Egan, B.M.; Hunt, K.J.; Smith, E.A. Raynaud phenomenon and mortality: 20+ years of follow-up of the Charleston Heart Study cohort. *Clin. Epidemiol.*, **2015**, *7*, 161-168.  
<http://dx.doi.org/10.2147/CLEP.S75482> PMID: 25678814
- [59] Rajagopalan, S.; Pfenninger, D.; Somers, E.; Kehrler, C.; Chakrabarti, A.; Mukherjee, D.; Brook, R.; Kaplan, M.J. Effects of cilostazol in patients with Raynaud's syndrome. *Am. J. Cardiol.*, **2003**, *92*(11), 1310-1315.  
<http://dx.doi.org/10.1016/j.amjcard.2003.08.013> PMID: 14636909
- [60] Negrini, S.; Spanò, F.; Penza, E.; Rollando, D.; Indiveri, F.; Filaci, G.; Puppo, F. Efficacy of cilostazol for the treatment of Raynaud's phenomenon in systemic sclerosis patients. *Clin. Exp. Med.*, **2016**, *16*(3), 407-412.  
<http://dx.doi.org/10.1007/s10238-015-0370-5> PMID: 26088182
- [61] Zheng, H.; Yang, H.; Gong, D.; Mai, L.; Qiu, X.; Chen, L.; Su, X.; Wei, R.; Zeng, Z. Progress in the Mechanism and Clinical Application of Cilostazol. *Curr. Top. Med. Chem.*, **2019**, *19*(31), 2919-2936.  
<http://dx.doi.org/10.2174/1568026619666191122123855> PMID: 31763974
- [62] Pletal 50 mg tablets summary of product characteristics. Available at: <https://www.medicines.org.uk/emc/product/164/smpc#companyDetails> (accessed on: 24 March, 2021)
- [63] Wigley, F.M. Treatment of Raynaud phenomenon: initial management, Available at: <https://www.uptodate.com/contents/treatment-of-raynaud-phenomenon-initial-management> (accessed on: 24 March, 2021)