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1 **Far-Infrared Therapy for Cardiovascular, Autoimmune, and**  
2 **Other Chronic Health Problems: A Systematic Review**

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33 **Abstract:** Physical therapy (physiotherapy), a complementary and alternative medicine therapy, has been  
34 widely applied in diagnosing and treating various diseases and defects. Increasing evidence suggests that  
35 convenient and noninvasive far-infrared (FIR) rays, a vital type of physiotherapy, improve the health of patients  
36 with cardiovascular disease, diabetes mellitus, and chronic kidney disease. Nevertheless, the molecular  
37 mechanisms by which FIR functions remain elusive. Hence, the purpose of this study was to review and  
38 summarize the results of previous investigations and to elaborate on the molecular mechanisms of FIR therapy  
39 in various types of disease. In conclusion, FIR therapy may be closely related to the increased expression of  
40 endothelial nitric oxide synthase as well as nitric oxide production and may modulate the profiles of some  
41 circulating miRNAs; thus, it may be a beneficial complement to treatments for some chronic diseases that yields  
42 no adverse effects.

43 **Keywords:** physical therapy, far-infrared (FIR), cardiovascular disease (CVD), diabetes mellitus (DM), miRNA

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45 **Running title:** Far-Infrared Therapy for Chronic Diseases

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51    **1 Introduction**

52    Infrared radiation is an invisible form of electromagnetic energy, the wavelength of which is  
53    longer than that of visible light. Infrared radiation can be categorized into 3 groups according  
54    to wavelength, namely near infrared (NIR, 0.8–1.5  $\mu\text{m}$ ), middle infrared (MIR, 1.5–5.6  $\mu\text{m}$ ),  
55    and far infrared (FIR, 5.6–1000  $\mu\text{m}$ ).<sup>1</sup> Infrared radiation probably enables multiple forms of  
56    energy to be transferred into subcutaneous tissue (approximately 2 to 3 cm deep) without  
57    stimulation or excessive heating.<sup>2</sup> In one study, skin temperature increased to 38–39°C after  
58    FIR treatment for 30 min to 1 h with 20 cm of spacing between ceramic plates and the skin.<sup>3</sup>  
59    Thus, FIR therapy may yield none of the side effects of traditional thermal therapy, such as  
60    infection or burn injury, and has therefore been widely employed to promote health.

61       FIR treatment methods can be divided into two categories according to clinical  
62    implementation in general. In the first category, an FIR emitter composed of electrified  
63    ceramic plates is placed 20 cm above a patient and provides low energy to increase skin  
64    temperature steadily.<sup>3</sup> In addition, the FIR radiator is frequently used in experiments for local  
65    (or point) treatment by maintaining the surface temperature lower than 40°C. In the other more  
66    prevalent category, FIR dry sauna therapy,<sup>4</sup> light is employed to create heat by using a sauna.  
67    Unlike traditional saunas, which apply heat to warm the body by increasing the ambient air  
68    temperature, FIR saunas heat the body directly without employing the air as a heat transfer  
69    medium.<sup>5</sup> In a previous study, sauna therapy was performed using an FIR dry sauna device at  
70    60°C for 15 min, followed by traditional warm keeping for 30 min.<sup>6</sup>

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71        Although previous studies have shown that FIR radiation produces thermal and  
72        nonthermal effects, such as increasing artery blood flow<sup>7</sup> and peripheral blood circulation,<sup>8</sup>  
73        improving endothelial function,<sup>9</sup> alleviating fatigue<sup>10</sup> and pain,<sup>11</sup> reducing blood pressure,<sup>12</sup>  
74        and promoting capillary dilatation,<sup>13</sup> the precise mechanism has yet to be thoroughly  
75        understood. Therefore, the purposes of this study were to review and summarize published  
76        data on FIR therapy on different types of disease (Table 1) and to delineate the mechanisms of  
77        FIR therapy.

78        **2 FIR Therapy for Cardiovascular Disease**

79        *2.1 Cardiovascular Disease*

80        Cardiovascular disease (CVD), the leading cause of deaths worldwide, refers to any disease  
81        affecting the cardiovascular system including cerebral and renal vascular diseases, cardiac  
82        disease, and peripheral arterial disease.<sup>14</sup> The most common factors that induce CVD are  
83        atherosclerosis and hypertension. Moreover, even in healthy asymptomatic elderly people,  
84        various alterations in physiology and morphology affect cardiovascular function and thus  
85        result in an increased risk of CVD;<sup>15</sup> thus, determining treatments for curing the disease is  
86        imperative.

87        *2.2 Effects of FIR on CVD*

88        Evidence has indicated that FIR rays exert protective effects on CVD. Several weeks of sauna  
89        therapy markedly enhanced flow-mediated endothelium-dependent dilation of the brachial  
90        artery ( $P < 0.001$ ),<sup>16-18</sup> which was associated with an increase in cardiopulmonary exercise  
91        tolerance.<sup>17,18</sup> Because endothelial dysfunction is typically observed in patients with

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92 hypertension,<sup>19</sup> hypercholesterolemia,<sup>20</sup> diabetes mellitus (DM),<sup>21</sup> and obesity and patients  
93 who smoke,<sup>22</sup> sauna treatments probably play a therapeutic role for patients with coronary risk  
94 factors, suggesting that sauna treatments improve vascular endothelial function.

95 Compelling evidence has indicated that vascular endothelial function is closely  
96 associated with endothelial nitric oxide synthase (eNOS), which catalyzes the amino acid  
97 L-arginine into L-citrulline and nitric oxide (NO) in the endothelium. NO is a crucial  
98 vasodilator substance, which prevents the progression of atherosclerosis by dilating blood  
99 vessels and inhibiting some arterial disorders such as platelet aggregation and the migration  
100 and proliferation of smooth muscle cells.<sup>23</sup> Ikeda et al. reported that 1 month of FIR sauna  
101 therapy significantly upregulated eNOS mRNA and protein expression ( $0.73 \pm 0.04$  vs.  $1.02 \pm$   
102  $0.02$ ,  $P < 0.01$ ;  $3250 \pm 70$  vs.  $4090 \pm 60$ ,  $P < 0.01$ , respectively) as well as serum NO  
103 production ( $3.98 \pm 0.43$  mmol/L vs.  $4.66 \pm 0.5$  mmol/L,  $P < 0.05$ ) in cardiomyopathic hamsters  
104 with chronic heart failure (CHF).<sup>24</sup> In addition to enhancing eNOS expression, FIR increases  
105 NO production probably by promoting the  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II  
106 (CaMKII)-mediated phosphorylation of eNOS at serine 1179 to increase eNOS activity.<sup>25</sup>  
107 Although FIR radiation can notably increase the temperature of culture media and  
108 intracellular  $\text{Ca}^{2+}$  levels, temperature-sensitive calcium channels and transient receptor  
109 potential vanilloid may not contribute to the pathway of the CaMKII-mediated  
110 phosphorylation of eNOS.<sup>25</sup> Thus, we propose that the nonthermal effects of FIR radiation, as  
111 has been recently shown for other types of nonionizing radiation,<sup>26</sup> may be involved in this  
112 pathway by activating voltage-gated calcium channels.<sup>27</sup> Nevertheless, all of these

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113 mechanisms suggested that upregulating NO production by increasing eNOS expression level  
114 and its phosphorylation level is a critical manner in which FIR therapy improves endothelial  
115 function in patients with CHF.

116 Notably, urinary 8-epi-prostaglandin F<sub>2α</sub> (a product of lipid peroxidation) levels were  
117 markedly lower in participants with coronary risk factors who received an FIR dry sauna for 2  
118 weeks compared with those of controls.<sup>28</sup> Because 8-epi-prostaglandin F<sub>2α</sub> is a reliable marker  
119 of oxidative stress in vivo, and oxidative stress is involved in the development of  
120 atherosclerosis and heart failure,<sup>29</sup> the results suggested that repeated FIR ray therapy can  
121 reduce oxidative stress,<sup>30</sup> preventing the progression of atherosclerosis. Because oxidative  
122 stress reduces the bioavailability of NO (free radicals can inactivate NO),<sup>31</sup> a reduction in  
123 oxidative stress probably indicates an improvement in endothelial function through an  
124 increase in NO production.

125 The enhancement in eNOS expression caused by FIR stimulation may be related with  
126 miRNA. Shear stress is crucial to increasing eNOS activity by stimulating its expression.<sup>32</sup> All  
127 of the aforementioned studies have suggested that FIR therapy accelerates peripheral blood  
128 flow, leading to an increase in shear stress, followed by increases in eNOS activity and NO  
129 production and upregulation of eNOS expression. Consequently, vascular endothelial function  
130 and exercise tolerance are improved.

131 A previous study reported that miRNAs are essential for various CVDs because  
132 depletion in the miRNA-processing enzyme engenders defects in cardiac development and  
133 angiogenesis.<sup>33</sup> Several studies have revealed that shear stress or FIR can regulate the

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134 expression of miRNAs in endothelial cells. For instance, miRNA-21 induced by shear stress  
135 in endothelial cells can modulate endothelial cell apoptosis and eNOS activity as well as NO  
136 production.<sup>34</sup> In one study, miRNA-663 played vital roles in shear stress-induced  
137 inflammatory responses by derepressing inflammatory response genes.<sup>35</sup> A recent study  
138 determined that FIR treatment enhanced the expression of miRNA-31 and miRNA-720,  
139 thereby increasing coronary artery disease endothelial progenitor cell (EPC) expression and  
140 rescuing the angiogenic and vasculogenic abilities of EPCs both in vitro and in vivo.<sup>36</sup>  
141 Circulating miRNAs (e.g., miRNA-1, miRNA-17, miRNA-92a, miRNA-126, miRNA-133,  
142 and miRNA-145) in the blood cells or serum/plasma have been identified as potential  
143 biomarkers of CVD<sup>37</sup> and can be used for diagnosing and determining the prognosis of acute  
144 myocardial infarction.<sup>38</sup> In summary, we suspect that FIR improves the endothelial function  
145 of patients with CVD by increasing eNOS and NO levels by promoting shear stress and  
146 altering the expression profiles of some circulating miRNAs.

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### 148 **3 FIR Therapy for Diabetes Mellitus**

#### 149 *3.1 Diabetes Mellitus*

150 **DM is a group of metabolic diseases caused either by a deficiency in insulin production (Type**  
151 **1) or by development of insulin resistance (Type 2).**<sup>39</sup> Most diabetes cases can be grouped into  
152 two broad etiopathogenetic categories: type 1 DM, caused by failure of the pancreas to secrete  
153 insulin; and type 2 DM, caused by the inability of the body to respond properly (e.g., resistance)  
154 to insulin action or insulin secretory response.<sup>40</sup> A person with DM (type 1 or 2) has high

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155 concentrations of blood sugar, which undermine the blood vessels, nerves, kidneys, and other  
156 systems of the body.<sup>40</sup>

157 *3.2 Effects of FIR on DM*

158 Masuda et al. demonstrated that repeated dry sauna therapy by using FIR reduced urinary  
159 levels of 8-epi-prostaglandin F<sub>2α</sub> (an oxidative stress marker)<sup>28</sup> and that DM was associated  
160 with increased oxidative stress,<sup>41</sup> which has a marked insulin-resistance effect.<sup>42</sup> Kawaura et  
161 al. investigated the oxidative-stress-related modulatory effect of FIR local stimulation in  
162 bedridden patients with type 2 DM.<sup>43</sup> Two weeks of local FIR therapy administered to the  
163 legs significantly reduced plasma 8-epi-prostaglandin F<sub>2α</sub> levels in type 2 DM patients ( $P <$   
164 0.05).<sup>43</sup> A reduction in eNOS bioactivity was involved in the pathogenesis of oxidative stress  
165 in skeletal muscle insulin resistance.<sup>44</sup> Furthermore, eNOS played a critical role in regulating  
166 insulin sensitivity.<sup>45</sup> Overall, FIR therapy may improve skeletal muscle insulin resistance  
167 through eNOS expression following a decrease in oxidative stress in patients with type 2 DM.

168 Patients with DM sustain stress because of daily dietary restrictions, leading to an  
169 excessive release of cortisol, causing diverse negative reactions such as hypertension.<sup>46</sup>  
170 Consequently, DM is exacerbated. Ryotokuji et al. indicated that 4 weeks of FIR radiation  
171 administered to the feet of type 2 DM patients significantly reduced cortisol levels and blood  
172 glucose levels.<sup>47</sup> Therefore, assuming that FIR therapy normalizes blood glucose levels by  
173 reducing serum levels of cortisol (adrenal glucocorticoid hormones) and thereby improves the  
174 ability to respond to insulin action in patients with type 2 DM is reasonable.

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175 Huang et al. observed that FIR therapy increased blood flow recovery by 48%, increased  
176 bone marrow-derived EPC differentiated into endothelial cells ( $11.2 \pm 1.1/\text{HPF}$  vs.  $18.8 \pm$   
177  $2.0/\text{HPF}$ ,  $P < 0.01$ ), and reduced oxidative stress ( $P < 0.05$ ) in streptozotocine-induced  
178 diabetic mice.<sup>48</sup> Moreover, the benefits of local FIR radiation were abolished after injection  
179 with L-NAME (an eNOS inhibitor).<sup>48</sup> Because neovascularization requires  
180 bone-marrow-derived circulating EPCs for vasculogenesis,<sup>49</sup> high glucose-impaired  
181 capacities of EPCs probably involve NO-related mechanisms.<sup>50</sup> In addition, NO can modify  
182 the mobilization and differentiation of EPCs,<sup>51</sup> and an increase in free radicals in tissue  
183 ischemia may downregulate NO bioavailability by directly inactivating NO.<sup>31</sup> Thus, FIR  
184 treatment may be related to a NO-related pathway. Moreover, FIR therapy is suggested to  
185 have benefits of promoting blood flow recovery and forming new vessels by enhancing the  
186 EPC homing process by reducing oxidative stress in the ischemic hindlimbs of diabetic mice.

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#### 188 **4 FIR Therapy for Chronic Kidney Disease**

##### 189 *4.1 Chronic Kidney Disease*

190 Chronic kidney disease (CKD) is a progressive renal dysfunction experienced during several  
191 months or years<sup>52</sup> and can be classified into 5 stages (stages 1 to 5) according to severity.  
192 End-stage renal disease (ESRD) is stage 5 CKD and is a severe illness with a poor prognosis  
193 for which treatment with dialysis or transplantation may be required.<sup>52</sup> For patients with  
194 ESRD who receive hemodialysis (HD) treatment, native arteriovenous fistulas (AVFs) and

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195 prosthetic arteriovenous grafts (AVGs)<sup>53</sup> are typically used to obtain the well-functioning  
196 vascular access that is critical to sufficient dialysis.<sup>54</sup>

197 *4.2 Effects of FIR on CKD*

198 Lin et al. showed that long-term FIR exposure increased access flow (Qa), reduced the  
199 incidence and relative incidence of AVF malfunction, and improved the unassisted patency of  
200 AVFs in HD patients.<sup>55</sup> Because decreasing vascular access flow (Qa) is an effective index for  
201 estimating thrombosis-related access dysfunctions,<sup>56</sup> the improvement in the patency of AVFs  
202 was likely associated with a higher value of Qa. According to Kipshidze et al.,<sup>57</sup> a nonablative  
203 infrared laser (NIL) restrained neointimal hyperplasia and reduced the proliferation of  
204 vascular smooth muscle cells (VSMCs) after percutaneous transluminal coronary angioplasty  
205 in cholesterol-fed rabbits for 60 days. Because the growth of VSMCs increases the risk of  
206 vascular access stenosis in HD patients,<sup>58</sup> inhibiting neointimal hyperplasia may be one  
207 mechanism through which FIR therapy improves vascular restenosis progression in patients  
208 with ESRD.

209 Furthermore, Lai et al. investigated the effect of FIR treatment on HD access maintenance  
210 after percutaneous transluminal angioplasties (PTAs) in AVG and AVF populations.<sup>59</sup> The data  
211 showed that a radiated group of patients with AVGs exhibited significantly improved  
212 unassisted patency at 1 year (16.3% vs. 2.1%,  $P < 0.05$ ).<sup>59</sup> However, in the AVF population,  
213 post-PTA FIR radiation therapy nonsignificantly improved the unassisted patency rate.<sup>59</sup> The  
214 results of clinical trials of FIR radiation therapy were inconsistent with those of Lin et al.,<sup>55</sup>  
215 possibly because most patients examined by Lin et al. received no PTA treatment.<sup>55</sup> Overall,

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216 because of the improvement in unassisted patency, FIR radiation therapy may benefit  
217 PTA-treated AVG and AVF patients who are high-functioning or have not received repeated  
218 PTA.

219 The failure of an AVF to mature is a critical pathologic reason for the malfunction of  
220 newly created AVFs in people at advanced stages of CKD.<sup>60</sup> Lin et al. reported that 3 months  
221 of FIR treatment can enhance the rate of AVF maturation significantly (90% vs. 76%,  $P <$   
222 0.05).<sup>61</sup> In addition, they demonstrated that FIR stimulation provided substantial benefits of  
223 increasing access flow and the rates of AVF unassisted patency and clinical maturation as  
224 well as lowering AVF malfunction within 1 year compared with controls.<sup>61</sup> These results were  
225 identical to those of their previous study.<sup>55</sup> Endothelial dysfunction associated with AVF  
226 stenosis may lead to AVF maturation failure in HD patients.<sup>58</sup> In summary, FIR benefitted HD  
227 patients by promoting endothelial function in both animal<sup>3,7,24</sup> and clinical studies.

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## 229 **5 FIR Therapy for Ischemia**

### 230 *5.1 Ischemia*

231 Ischemia that triggers the unavailability of oxygen and glucose to tissues is generally ascribed  
232 to blood vessel problems, resultant damage, or tissue dysfunction. If not treated immediately,  
233 ischemia may aggravate rapidly to tissue necrosis and gangrene within several hours,  
234 potentially leading to paralysis.<sup>62</sup>

### 235 *5.2 Effects of FIR on Ischemia*

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236 A previous study determined that FIR radiation provides a strong antiinflammatory benefit to  
237 the vascular endothelium by inducing heme oxygenase-1 (HO-1) expression.<sup>63</sup> HO-1 is a  
238 rate-limiting enzyme in heme oxidization of biliverdin and carbon monoxide.<sup>64</sup> Biliverdin can  
239 be further catalyzed to a potent antioxidant bilirubin,<sup>65</sup> whereas carbon monoxide, similar to  
240 NO, exhibited effects of vasodilation and modulating intracellular cGMP levels in one  
241 study.<sup>66</sup> Thus, FIR probably plays a crucial role in increasing cGMP signaling. HO-1 was  
242 shown to prevent testis injury in models of hypoxic preconditioning.<sup>67</sup> Tu et al. investigated  
243 the effect of FIR postconditioning on ischemia/reperfusion (I/R) injury in rat testes.<sup>68</sup> The  
244 results indicated that HO-1 protein in the testes was overexpressed in a group of rats with 2  
245 h-ischemia I/R injury treated with FIR ray therapy for 30 min compared with untreated and  
246 heat light groups.<sup>68</sup> In addition, administering an HO-1 inhibitor abolished the effect of FIR  
247 treatment.<sup>68</sup> Furthermore, FIR therapy drastically reduced apoptosis and alleviated injury of  
248 testis tissue,<sup>68</sup> suggesting that HO-1 is crucial in FIR postconditioning for protecting rat testis  
249 from I/R injury.

250 In a mouse model of an ischemic hindlimb, Akasaki et al. reported that 5 weeks of FIR  
251 sauna therapy markedly upregulated blood flow, capillary density, eNOS expression, and NO  
252 production compared with those of controls.<sup>7</sup> However, administering L-NAME suppressed  
253 the effects induced by FIR stimulation.<sup>7</sup>

254 FIR alleviated tissue ischemia in animal<sup>3,7,68</sup> and clinical studies.<sup>69</sup> Tei et al. reported that  
255 long-term sauna therapy reduced pain scores, increased blood flow, and promoted

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256 angiogenesis,<sup>69</sup> but was ineffective in eNOS-deficient mice. In addition, exercise tolerance  
257 was upregulated.<sup>69</sup>

258 The induction of NO by eNOS is essential for regulating angiogenesis,<sup>70</sup> and this process  
259 can be elicited by vascular endothelial growth factor.<sup>71-73</sup> In summary, eNOS is a critical  
260 regulator for angiogenesis in repeated FIR sauna therapy. In addition, both eNOS and  
261 exercise can increase the mobilization of EPCs,<sup>51,69</sup> which is vital to vasculogenesis.<sup>48</sup> Thus,  
262 FIR may be a novel innovative therapy for treating ischemic areas.

263 Successful revascularization of an ischemic region necessitates new blood vessel growth,  
264 stabilization, and maturation,<sup>74,75</sup> which are critical for reducing cell death and increasing the  
265 blood supply to damaged areas.<sup>76</sup> Because of the importance of pericytes in maintaining  
266 newly generated microvessels during angiogenesis, pericyte deficiency leads to endothelial  
267 cell apoptosis and destabilization of the microvasculature.<sup>77</sup> Thus, pericyte recruitment likely  
268 plays a key role in vascular remodeling in cortical tissues after ischemic stroke. Furthermore,  
269 a recent study reported that pericyte relaxation increased blood flow *in vivo*.<sup>78</sup> Because FIR  
270 rays enhance blood flow and improve ischemic areas, although the exact mechanism has not  
271 been elucidated, we speculate that FIR rays positively affect pericytes after ischemia.

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## 273 **6 FIR Therapy for Other Diseases**

274 FIR therapy is effective in relieving pain in patients with chronic pain,<sup>79</sup> chronic fatigue  
275 syndrome,<sup>80</sup> and fibromyalgia.<sup>81,82</sup> FIR benefitted trained runners who suffered from muscle  
276 damage<sup>83</sup> and patients who experienced persistent and progressively increasing phantom limb

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277 pain after amputation.<sup>84</sup> Furthermore, FIR stimulation alleviated depression in patients with  
278 insomnia by increasing serotonin and reducing malondialdehyde levels.<sup>85</sup> However, a case of  
279 pseudolymphoma occurring in a blue-green tattoo was thought to be related to FIR light  
280 exposure and induced sweating.<sup>86</sup> These effects on living organisms exposed to FIR rays are  
281 poorly understood; therefore, further study is required.

282

## 283 **7 Conclusion and Perspectives**

284 As a potential complementary therapy, FIR radiation had both thermal and nonthermal effects.  
285 The thermal effect of FIR therapy could increase blood flow and vasodilation by heating the  
286 tissue (hyperthermia), similar to ordinary thermal therapy composed of heat pads or hot  
287 water.<sup>87</sup> In addition, FIR treatment with low levels of delivered energy (nonthermal effect)  
288 also had biological activities.<sup>88,89</sup> A study of patients receiving hemodialysis treatment had  
289 shown decreases in stress and fatigue levels by FIR stimulation rather than thermal treatment  
290 (heat pads), which was probably attributed to the nonthermal effect.<sup>10</sup> A explanation of  
291 nonthermal effect of such low energy levels was that nanoscopic water layers got disturbed  
292 by low irradiances, leading to the change of cellular membrane structure, then made the  
293 therapeutic effects.<sup>87</sup>

294 Since FIR therapy was frequently applied in the medical field, numerous investigators  
295 have attempted to determine the effects of these novel FIR rays on biological systems. FIR  
296 radiation has multiple properties; thus, no direct interrelationships among the properties could  
297 be identified. Possible explanations include reduction in oxidative stress, improvement in

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298 endothelial function, and inhibition of neointimal hyperplasia. Regarding the effect of FIR  
299 treatment on oxidative stress downregulation, Masuda et al. showed that FIR therapy reduced  
300 oxidative stress in patients with coronary risk factors.<sup>28</sup> In addition, a decrease in oxidative  
301 stress was observed in DM patients who received FIR therapy.<sup>41,48</sup> Regarding the effect on  
302 endothelial function, an intervention group exposed to FIR rays exhibited quicker  
303 amelioration of endothelial function than did nonexposed controls in both CVD<sup>16</sup> and CKD  
304 populations.<sup>61</sup> Regarding the third mechanism, Kipshidze et al. demonstrated that NIL  
305 inhibited neointimal hyperplasia.<sup>57</sup>

306 Furthermore, FIR rays have been applied in treating various chronic diseases, such as  
307 hypertension, heart failure, and vascular endothelial dysfunction, which are associated with  
308 the depletion of tetrahydrobiopterin (BH4), a critical cofactor for NO synthases.<sup>90,91</sup> FIR  
309 therapy improves blood flow in heated surface areas, causing an increase in vascular shear  
310 stress and enhancement of the activity of GTP cyclohydrolase I, which benefits BH4  
311 synthesis.<sup>92,93</sup> Thus, the increased availability of BH4 may provide key insight into the  
312 underlying mechanisms of sauna therapy. A recent study demonstrated that capillaries control  
313 blood flow primarily related to active pericyte relaxation.<sup>78</sup> In addition, pericyte death in rigor  
314 results in a permanent decrease in blood flow in capillaries and damages neurons after  
315 stroke.<sup>94-96</sup> These mechanisms resemble FIR in improving capillary dilation and blood flow  
316 and may reflect the promotion of stroke recovery by FIR stimulation. In other words, FIR  
317 therapy may alleviate stroke by inhibiting pericyte death.

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318 Except for the aforementioned mechanisms, the eNOS and NO-increasing activity of FIR  
319 radiation treatment may be recognized as a possible common background (Fig. 1).<sup>97</sup> An  
320 increase in blood flow induced by FIR treatment increases shear stress, which is a crucial  
321 determinant of endothelial function and phenotype in atherosclerosis. Furthermore, previous  
322 evidence has shown that shear stress regulated the expression of miRNAs in endothelial cells,  
323 and miRNAs influence endothelial biology by reducing apoptosis and activating the NO  
324 pathway.<sup>34</sup> Therefore, FIR therapy is a potential therapeutic method for treating CVD because  
325 it increases shear stress by regulating the expression of miRNA. Overall, FIR ray treatment  
326 accelerates peripheral blood flow, leading to an increase in shear stress; consequently, the  
327 miRNA levels are elevated, followed by an increase in eNOS and NO production.

328 The expression of NOS activity and miRNA has a circadian rhythm and is closely  
329 associated with control mechanisms governing circadian expression. Ayers et al. reported that  
330 NOS activity in the kidneys of mice exhibited a clear circadian variation. The highest level  
331 occurred during the dark period and the lowest level occurred during the light period.<sup>98</sup> In  
332 addition, NOS activation mediated the phase-shifting effects of melatonin and  
333 5-hydroxytryptamine on a suprachiasmatic nuclei (SCN) circadian pacemaker in rats.<sup>99</sup>  
334 Moreover, as key regulators of the circadian timing process, miRNA-219 and miRNA-132  
335 levels in SCN exhibited a salient rhythm, the highest level of which occurred during the  
336 subjective day.<sup>100</sup> In addition, several miRNAs are involved in the modulation of the  
337 peripheral circadian rhythm in mouse livers.<sup>101,102</sup> Circadian rhythms have been observed in  
338 the incidences of cerebrovascular diseases, arterial diseases, and ischemic stroke.<sup>103,104</sup> These

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339 results suggested that the diurnal variation of NOS and miRNAs may be related with that of  
340 the onset of some chronic diseases. Therefore, FIR rays may have striking therapeutic effects  
341 on medical treatments on the basis of a circadian rhythm. However, further research  
342 considering objective parameters and sufficient sample sizes must be conducted in animal  
343 models and clinical applications to completely reveal the functional effect of circadian  
344 rhythms on FIR rays.

345

346 *Author Contributions*

347 LZ provided ideas and research directions; SSs wrote the sections on FIR therapy for CVD,  
348 FIR therapy for DM, and FIR therapy for CKD; XW wrote the sections on FIR therapy for  
349 ischemia and FIR therapy for other diseases; and JYC provided program support.

350

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649 Table and Figure Legends

650 **Table Legend**

651 FIR, far infrared; CVD, cardiovascular disease; FMD, flow-mediated endothelium-dependent dilation;

652 CHF, chronic heart failure; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; 6MWD,

653 6-minute walk distance; DM, diabetes mellitus; EPC, endothelial progenitor cell; ESRD, end-stage renal disease;

654 Qa, access flow; AVF, arteriovenous fistula; CKD, chronic kidney disease; AVG, arteriovenous graft;

655 PTA, percutaneous transluminal angioplasty; PAD, peripheral arterial disease; HO-1, heme oxygenase-1.

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657

658 **Figure Legend**

659 Effects of far-infrared therapy. Far-infrared (FIR) rays enable multiple energy transfer as deep as 2 to 3 cm into

660 subcutaneous tissue without irritating or overheating the skin and then accelerate blood flow, leading to an

661 increase in shear stress, followed by an increase in endothelial nitric oxide synthase activity and nitric oxide

662 production. Moreover, FIR or shear stress can regulate the expression of some circulating miRNAs in

663 endothelial cells. Consequently, FIR therapy improves the symptoms of chronic diseases (e.g., cardiovascular

664 disease, diabetes mellitus, and chronic kidney disease).

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