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REVIEW ARTICLE

Far-infrared Ray-mediated Antioxidant Potentials are Important for Attenuating Psychotoxic Disorders

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Abstract: Far-infrared ray (FIR) is an electromagnetic wave that produces various health benefits against pathophysiological conditions, such as diabetes mellitus, renocardiovascular disorders, stress, and depression *etc*. However, the therapeutic application on the FIR-mediated protective potentials remains to be further extended. To achieve better understanding on FIR-mediated therapeutic potentials, we summarized additional findings in the present study that exposure to FIR ameliorates stressful condition, memory impairments, drug dependence, and mitochondrial dysfunction in the central nervous system. In this review, we underlined that FIR requires modulations of janus kinase 2 / signal transducer and activator of transcription 3 (JAK2/STAT3), nuclear factor E2-related factor 2 (Nrf-2), muscarinic M1 acetylcholine receptor (M1 mAChR), dopamine D1 receptor, protein kinase C δ gene, and glutathione peroxidase-1 gene for exerting the protective potentials in response to neuropsychotoxic conditions.

Keywords: Far-infrared ray, nuclear factor E2-related factor 2, glutathione peroxidase-1, JAK2/STAT3, M1 mAChR, dopamine D1 receptor, protein kinase C δ gene, neuropsychotoxic conditions.

1. INTRODUCTION

1.1. Preview of Far-infrared ray

Infrared ray is an invisible spectrum of an electromagnetic wave used for the treatment of several discomforts. Infrared ray spectrum has a longer wavelength than visible radiation, which ranges from 750nm-1000μm [1]. According to the International Commission on Illumination infrared ray has been classified into three different bands based on their wavelength, *i.e*., near-infrared ray (NIR) (0.7–1.4 μm), middle infrared ray (MIR) (1.4–3 μm), and far-infrared ray (FIR) (3–1000 μm) [1, 2]. Among them, FIR is widely accepted as a therapeutic tool for biomedical and healthcare applications [3, 4], because of its ability to evenly transfer energy in the form of heat [5, 6]. However, beneficial effects of NIR were also recognized in diverse fields such as agricultural/food, fuel industry, textile industry, and biomedical usage [7, 8]. Although NIR is absorbed at skin level and enhanced the temperature [9], FIR penetrates deep into the tissues and regulates molecular mechanism *via* resonating water molecules [1, 10]. Moreover, FIR therapy uses longer wavelengths than NIR therapy [10], FIR is absorbed by and emitted by the body as a black body radiation (*i.e*., FIR absorber; 3-50 μm with an output peak at 9.4 μm) [1]. Additionally, it has been suggested that FIR therapy may not cause side effects. Therefore, it has been widely used to potentiate beneficial health effects [11, 12].

In 1989, thermal therapy was developed by using FIR dry sauna. Since this differs from the traditional sauna, Tei *et al*. (2007) changed the name from "thermal therapy" to "Waon therapy" that uniformly maintained the temperature at 60°C. "Wa" means soothing, and "On" means warmth, hence Waon or "soothing warmth" [13, 14]. Under Waon therapy, patients were exposed to FIR for 15 min, which steadily and uniformly warm the body, after which patients were allowed to rest outside the sauna under the blanket to maintain warmth for additional 30 min [14].

There are three main therapeutic techniques used to convey FIR [1]: i) FIR saunas; they are frequently used in Japan

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as "Woan therapy", in this light is placed to create and transfer heat purely as a radiant heat, *i.e*., without using air as a medium [1, 15], ii) FIR devices; consist of electrified ceramic plates, placed at 20-30cm above patient [16] and iii) FIR emitting ceramics and fabrics; they work as a perfect absorber of heat from skin and then transfer heat back to the skin [1, 17]. Moreover, under standard experimental condition animals were exposed to FIR by using FIR emitting panel positioned at 40cm above the animal, and emit FIR ranging from wavelength 5-20 μm with controlled surface temperature, *i.e*., 40 °C [18-22]. Importantly, bioceramics including FIR emitters, increased nitric oxide (NO) production [1, 11], and facilitated microcirculation [23, 24]. FIR emitted by tourmaline powder has been shown to enhance blood flow in skin [25, 26]. In addition, bioceramic belts are readily used for attenuating renal disorder [16]. Bioceramic socks are used to treat chronic foot pain in diabetic neuropathy [27]. Soccer players have used FIR emitting clothing to relieve muscle pain [28]. In addition, several commercial centers are available that sell beds made of jades that convert light from helium projector bulbs into FIR [9].

Therapeutic effects of FIR have well-recognized against several pathophysiological conditions [1, 11, 29, 30], such as diabetes mellitus [11], chronic heart failure [11, 31], chronic kidney disease [11, 16, 32], stress [21], and depression [33]. Exposure to FIR stimulates oxygenation and sweating within the body [1, 34], which might be essential for detoxification and elimination of impurities. FIR therapy also helps in reducing body weight [35, 36], and life-style related diseases (such as, hypertension, hyperlipidemia, and smoking) [36]. Therefore, the purpose of the review is to summarize the possible underlying mechanisms of FIR-mediated therapeutic potentials against cardiovascular and psychotoxic disorder (Table **1**).

Cardiovascular disease (CVD) is a combination of heart and blood vessels disorders, including coronary heart disease, cerebrovascular disease, renal vascular disease, and congenital heart diseases [37, 38]. Because of its severity, CVD is a leading cause of mortality globally. Hypertension, atherosclerosis, diabetes, smoking, and obesity are some of the consistent risk factors for CVD [39, 40]. Clinical studies revealed that FIR therapy protects against CVD. In particular, it was demonstrated that FIR-dry sauna improves endothelial functions in patients with CVD risk factors [41]. Escalating evidence suggested that endothelial nitric oxide synthase (*eNOS*) plays a critical role in FIR-mediated protective potentials against CVD risk factors [11, 41]. eNOS catalyzes the conversion of L-arginine into L-citrulline with the release of nitric NO, a crucial vasodilator molecule, which prevents atherosclerosis *via* vasodilation and inhibition of platelet aggregation [42]. It has been suggested that FIR therapy upregulate eNOS gene expression, and eventually generate NO [43]. Moreover, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is important for FIR-mediated induction of eNOS [44]. Increased peripheral blood flow by FIR therapy shears stress, which further induces eNOS and NO production.

Asahara *et al*. (1997) demonstrated that vasculogenesis involves bone marrow-derived endothelial progenitor cells (EPCs) [45], while CVD risk factors impair EPCs mediated functions [46]. miRNAs recognized as a potential biomarker for CVD [47]. Although it has been demonstrated that the decrease in miRNA alters the angiogenic process [48], miRNA-positively regulates eNOS activity and generates NO [49]. Exposure to FIR positively regulates miRNA in endothelial cells [50]. In particular, exposure to FIR attenuates vasculogenic abnormalities *via* up-regulation of miRNA-31 and miRNA-720, which may be essential for normalization of circulating EPCs expression and function [50]. In addition, Masuda *et al*. (2004) demonstrated that exposure to FIR significantly decreased the urinary lipid peroxidation marker (*i.e*., 8-epi-prostaglandin F2α) in CVD

Table 1. Protective potentials of FIR against pathophysiological conditions.

Model		Protective Effect	Underlying Molecular Parameters	Refs.
Ischemia	Hind limb (mouse)	Angiogenesis, vasculogenesis, and antioxidant potential	• eNOS ↑ • EPCs ↑ • HO-1 ↑	[67, 69]
Ischemia	Testicular (rat)	Attenuate I/R injury, decreases apoptosis	• HO-1 ↑	[65]
Cardiovascular disorder	Human	Improve endothelial function, antioxidant potential	• eNOS ↑ • NO ↑ • EPCs ↑ • miRNA-31 ↑ • miRNA-720 ↑ • Lipid peroxidation ↑	[41, 43, 44, 50]
Diabetes mellitus	Mouse and human	Antioxidant potentials	• Peripheral blood circulation↑ • Cortisol ↓ • Lipid peroxidation ↓	[51, 58-60, 62]

I/R injury; ischemia reperfusion injury, eNOS; endothelial nitric oxide synthase, HO-1; heme oxygenase-1, EPCs; endothelial progenitor cells, NO; nitric oxide.

risk factors patients [51], suggesting that exposure to FIR exhibits antioxidant potentials against CVD. Combined, these studies indicate that exposure to FIR can improve CVD *via* induction of eNOS, miRNA expression, and antioxidant activity.

The end-stage renal disease progressively leads to chronic renal failure and requires hemodialysis (HD) or kidney transplantation [52]. It has been demonstrated that exposure to FIR improve progressive renal dysfunction by increasing the access flow (Qa), while decreasing the malfunction of incidence and relative incidence of arteriovenous fistulas (AVFs) in HD patients [16]. Impaired growth of vascular smooth muscle cells might cause vascular stenosis. Moreover, failure of AVF maturation causes dysfunction of newly formed AVFs in patients with chronic kidney disease [53]. Exposure to FIR significantly improves AVFs maturation *via* attenuation of vascular restenosis in end-stage renal disease [11, 16, 53]. Additionally, it was demonstrated that exposure to FIR attenuates cisplatin-induced nephrotoxicity *via* inactivation of caspase-3 in HK-2 cells [54].

It has been demonstrated that FIR transmits thermal energy and improve AVF *via* vasodilation, while non-thermal effect includes antioxidant and anti-inflammatory potentials. Exposure to FIR attenuates TNFα-induced adhesion molecule E-selectin, vascular cell adhesion protein-1, and monocyte chemoattractant protein-1 [55]. Recently, it was reported that exposure to FIR inhibits IL-6 and TNF-α, while activates eNOS expression and vascular endothelial function [56]. In addition, Chen *et al*. (2016) showed that FIR-mediated induction of eNOS is essential for improving endothelial function, which is essential for increases in Qa and AVFs [12, 55]. These studies suggest that FIR therapy might be a potential therapeutic tool against end-stage renal disease.

Most common symptoms of diabetes mellitus (DM) are excessive thirst, hunger, urination, weakness, fatigue, nausea, and vomiting [57]. Importantly, FIR sauna therapy protects against DM and associated oxidative stress [51, 58]. Moreover, it has been reported that FIR-mediated leg hyperthermia attenuates oxidative stress in patients with type 2 DM [59]. Wang *et al*. (2016) demonstrated that high glucose may induce endothelial cell dysfunction, and that exposure to FIR attenuates this phenomenon in DM patients [60]. In addition, exposure to FIR attenuated advanced glycation end product (an oxidative parameter)-induced injury in vascular endothelial cells *via* activation of promyelocytic leukemia zinc finger protein [61].

In addition, FIR sauna therapy improved the quality of life in patients suffering from type 2 DM [62]. For example, FIR sauna significantly improved stress, fatigue, and pain in type 2 DM patients [62]. Importantly, it has been demonstrated that downregulation of eNOS causes oxidative damage in insulin-resistant skeletal muscle [63], and that eNOS is essential for the regulation of insulin sensitivity [64]. Therefore, it is plausible that FIR-mediated induction of eNOS might be involved in the protective mechanism against type 2 DM.

Ischemia is a restriction of blood supply to the tissues, results in energy deprivation because of unavailability of oxygen and glucose. It has been demonstrated that exposure to FIR alleviates ischemia-reperfusion injury in rat testes *via* induction of heme oxygenase-1 (HO-1) [65], a rate-limiting enzyme of that catalyzes the catabolism of heme to produce biliverdin and carbon monoxide [29]. Biliverdin further catabolized to a potent antioxidant, bilirubin [66], suggesting that HO-1 is a critical target for FIR mediated anti-ischemic potentials.

In addition, induction of eNOS is also essential for FIR-mediated anti-ischemic potentials. Akasaki *et al*. (2006) demonstrated that FIR sauna therapy alleviates hindlimb ischemia *via* induction of angiogenesis through eNOS [67]. Furthermore, L-NG-nitroarginine methyl ester (L-NAME; an eNOS inhibitor), or genetic depletion of eNOS counteracted the FIR-mediated protective potentials in response to the ischemic model [67]. Therefore, it is possible that FIR exerts anti-ischemic effects *via* inductions of HO-1 and eNOS.

Yue *et al*. (2011) suggested that the possible relation between circulating EPCs level and vasoconstriction is noted in patients with type 2 DM [68]. Furthermore, exposure to FIR increased bone marrow-derived EPCs, and therefore, exhibited antioxidative activity [69]. In addition, exposure to FIR potentiated vasculogenesis in hindlimb ischemia *via* antioxidant activity and induction of EPCs in mice [69].

It is well-recognized that revascularization in ischemia is essential for enhancing blood supply and consequently attenuates tissue damage [70]. Pericytes play a vital role for the maintenance of endothelial cells and microvasculature during angiogenesis [71], and relaxation of pericytes increases blood flow [72]. Thus, it may be speculated that exposure to FIR may modulate recruitment and relaxation of pericytes at the site of ischemia. To extend our knowledge, we summarized in this review on the possible underlying mechanism for FIR-mediated neuroprotective potentials against psychotoxic conditions (Table **2**).

2. FIR THERAPY IN RESPONSE TO NEURO-PSYCHOTOXIC CONDITIONS

2.1. FIR Therapy Attenuates Sleep Disorder and Depression

Sleeping disorder is characterized by less sleep, difficulty in sleeping, circadian rhythm disorders, and insomnia. Chronic insomnia might be a risk factor for neuropsychiatric problems such as, depression, anxiety, and substance abuse [73, 74], and could be a major cause of morbidity. Elderly people suffer from inadequate sleep because of less melatonin levels [75], which may further consequently increase the risk of sleep disorder.

It has been reported that exposure to FIR modulates sleep-waking pattern in freely moving rats and physical condition *via* facilitating blood circulation [76]. At present, little is known about the underlying mechanism on sleep enhancing potentials of FIR other than the tissue-warming efficacy. However, it is known that exposure to FIR improves peripheral blood circulation, and hence increases the metabolism in tissues [77]. In addition, FIR penetrates deep into the tissue up to 4 cm in depth [78], and resonates with water and other organic molecules in the body, which might generate thermal

Table 2. Protective potentials of FIR against diverse neuropsychotoxic conditions.

Model		Protective Mechanisms	Molecular Parameters	Refs.
Sleep disorder	Mouse and human	Sleep modulatory action	Possible thermal effect: • Peripheral blood circulation ↑ • Chemical-messenger system ↑	[76, 77]
Depressive disorder	Human	N/A	N/A	[87]
Depression	Insomnia (Human) Loss-appetite (Mouse)	Anti-depressive efficacy, antioxidant potential, psycho-somatic relaxation	• Serotonin ↑ • MDA ↓ • Plasma ghrelin ↓	[91, 92]
Stress	Psychological-stress (rat and frog)	normalize heart rate, and blood pressure	• Oxidative stress ↓ • Adrenaline ↓	[101]
Stress	Acute-restraint stress	Anti-stressful efficacy, and antioxidant potentials	• c-Fos ↓ • JAK2/STAT3 ↓ • Oxidative parameters ↓ • GPx-1gene ↑	[21]
Behavioral sensitization	Methamphetamine (mouse)	Attenuates Behavioral sensiti-zation *via* antioxidant poten-tials and recovery of mito-chondrial function	• c-Fos ↓ • Dopamine D1 receptor ↓ • Oxidative parameters ↓ • GPx-1gene ↑	[18]
Memory impairment	Methamphetamine (mouse)	Memory enhancing activity, antioxidant potentials	• Nrf2-dependent GSH system ↑ • M1 mAChR ↑ • p-ERK ↑ • PKCδ/p-PKCδ ↓	[19, 20]

Abbreviations: M1 mAChR; Muscarinic acetylcholine receptors, PKC; protein kinase C, Nrf2, nuclear factor E2-related factor 2; GSH; reduced glutathione, N/A; not available, GPx; glutathione peroxidase, JAK2; Janus kinase 2, STAT3; Signal transducer and activator of transcription3.

reactions, and optimally increases body temperature [3]. Moreover, studies on neuroimaging and magnetic resonance showed that exposure to FIR increases the motility of water molecules [77], which may further stimulate the penetration of water molecules into various tissues [41], and might cause an alteration in molecular mechanism responsible for sleep.

Depression is a major psychiatric disorder that reduces the quality of life and might cause insomnia [79-81], and emotional distress [82]. Depression is associated with alterations in cerebral blood flow [83], neurogenesis [84], endogenous antioxidant levels [85], and neurotransmitters [86]. Monoamine neurotransmitters (*i.e.*, serotonin, norepinephrine, and dopamine) play a major role in the progression of the depressive disorder and are involved in physiological functions, such as, sleep, suicidal attempt, cognition, and reward [87-89].

Exposure to FIR modulated serotonin levels in depressive patients with insomnia, and also decreased lipid peroxidation marker (*i.e.*, malondialdehyde) in serum. It has been proposed that oxidative stress might be responsible for mood disorders [90]. Therefore, it may be plausible that antioxidant activity might be involved in FIR-mediated anti-depressive effects [91]. In addition, Salehpour *et al*. (2017) demonstrated that transcranial photobiomodulation (PBM; consist of low-power lasers and light-emitting diodes in the far-red to near-infrared optical region) therapy is efficacious with negligible adverse effects against depressive disorder [87]. Furthermore, Masuda *et al*. (2005) reported that FIR sauna therapy is effective on depression and depression-induced lost appetite [92], and that FIR sauna therapy might protect against somatic and mental complaints *via* psycho-somatic relaxation [92]. In addition, exposure to FIR alleviated fatigue, headache, and myalgia [58], although underlying mechanism remains to be determined.

2.2. Anti-stress Efficacy of FIR

Stress is ubiquitously present in our daily life, leading to severe health problems, such as cardiovascular disease [93], obesity [94], and neuropsychiatric disorders [95]. Stressful condition can increase the risk of high blood pressure and myocardiac infraction [96] and also enhances sympathetic control, while reduces parasympathetic control [97]. Stress can stimulate the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, which is critical for stress-induced responses [98]. Stressful condition stimulates "fight-or-flight" response, which increases adrenaline release *via* activation of sympathetic nervous system [99]. Stress mediates oxidative stress *via* stimulation of several biological pathways. It has been dem-

onstrated that hydrogen peroxide (H_2O_2) decreases antioxidant system, and alters contractile force in the myocardium [100]. In contrast, Leung *et al*. (2012) showed that BIOCERAMIC (a far infrared ray emitter) protects against psychological stress-induced cardiac arrest and myocardiac infraction *via* normalizing the blood pressure and antioxidant activity by decrease in the adrenaline release [101].

Moreover, it was demonstrated that restraint stress induces oxidative burdens [18, 33, 102]. Cecatelli *et al*. (1989) showed that stressors activate c-Fos-immunoreactivity (c-Fos-IR) in neurons in the paraventricular nucleus of the hypothalamus (PVN) [103]. Consistently, we demonstrated that acute restraint stress (ARS) induces c-Fos-IR in PVN. Recently, we demonstrated that exposure to FIR significantly attenuates ARS-induced c-Fos-IR in PVN [21]. Importantly, we and others suggested that restraint stress significantly decreases the glutathione peroxidase (GPx) activity in the brain [21, 104]. Although GPx is a major antioxidant enzyme in the brain for detoxification of peroxides, the depletion reduced glutathione (GSH) causes downregulation of GPx [21, 105, 106]. Furthermore, a decrease in intracellular GSH causes an increase in oxidative parameters [*i.e*., reactive oxygen species (ROS), lipid peroxidation, and protein oxidation]. Thus, we proposed that exposure to FIR protects against ARS-induced oxidative damage *via* induction of GPx-1 gene [21].

In addition, it was recognized that janus kinase 2 / *signal transducer and activator of transcription 3* (JAK2/STAT3) signal pathway might play a role in inducing oxidative stress [107]. We showed that ARS significantly upregulated JAK2/STAT3 signal pathway, and hence produces oxidative burdens [21]. In contrast, exposure to FIR inactivates the JAK2/STAT3, but not NFkB, signaling pathway against ARS. These positive potentials of FIR against ARS were comparable to those mediated by genetic overexpression of GPx-1 [107]. Moreover, exposure to FIR-mediated eNOS induction might cause recovery of autonomic nervous activity [108]. Oelze *et al*. (2014) demonstrated that GPx-1 deficiency results in endothelial and vascular dysfunction [109]. Consistently, Ullrich and Kissner (2006) reported that positive modulation of eNOS requires activation of GPx-1 [110]. However, FIR-mediated increase in eNOS and GPx-1 levels against stressful condition needs to be elucidated. Here, we propose that FIR attenuates ARS-induced oxidative burdens *via* inhibition of JAK2/STAT3 and induction of GPx-1 gene.

2.3. FIR Therapy Attenuates Methamphetamine (MA)-induced Behavioral Sensitization

Escalating evidence suggested that repeated stressful condition enhances abusive potentials [111-113]. In particular, restraint stress facilitates MA-induced drug dependence *via* excitotoxicity and oxidative stress [112, 114, 115]. MA, a derivative of amphetamine, is a highly consumed illicit psychostimulant after cannabis [116]. MA is more addictive than amphetamine because of its long-lasting action. MA is highly lipid soluble and readily cross blood-brain barrier [117]. MA drug abuse is contributable to neurotoxicity, and psychosis including cognitive impairment. Symptoms of MA-induced psychosis are similar to those of schizophrenia, such as hallucination and delusion [118, 119]. Repeated low doses of MA cause behavioral sensitization [120, 121], whereas higher doses cause neurotoxicity [106, 122]. It is well-recognized that repeated MA treatment induces behavioral sensitization following withdrawal period [123-125]. Interestingly, aripiprazole (a well-known antipsychotic) protects against MA-induced behavioral sensitization [124, 126]. Consistently, exposure to FIR significantly attenuates MA-induced behavioral sensitization in mice [18].

MA treatment stimulates dopamine release, which might cause euphoria, enhanced mental acuity, and positive mood [127, 128]. It is well-recognized the essential role of dopamine in MA psychosis and behavioral sensitization [129, 130]. MA induces hypodopaminergic condition *via* depletion of presynaptic dopamine causes negative symptoms [131], this may cause recurrence of psychosis in response to MA. Furthermore, excessive dopamine oxidized to H_2O_2 by monoamine oxidases [132]. H_2O_2 further detoxified by mitochondrial GPx to produce H_2O [133]. Additionally, impaired homeostasis in enzymatic antioxidants between GPx and superoxide dismutase (SOD) might also cause behavioral sensitization because of increased oxidative stress [134]. In addition, we demonstrated that MA treatment increases SOD activity, which might be responsible for the accumulation of H_2O_2, and finally potentiates oxidative stress [122]. In our recent study, we demonstrated that repeated MA treatment leads to behavioral sensitization *via* upregulation of dopamine D1 receptor and down-regulation of GPx-1 gene. Importantly, exposure to FIR significantly attenuates MA-induced SOD activity, while inducing GPx level [18].

Protective potentials of dopamine D1 or D2 receptor antagonists against MA-induced behavioral sensitization have been well recognized [135, 136]. Genetic depletion of dopamine D2 receptor attenuates MA-induced sensitization [137]. In addition, it has been demonstrated that genetic depletion of adenylyl cyclase 1 and 8 subtypes inhibits MA-induced behavioral sensitization and activation of 'dopamine and cAMP-regulated phosphoprotein-32 (DARPP-32)' indicating that activation of cAMP/PKA system is important for the behavioral sensitization [138]. Exposure to FIR protects against MA-induced behavioral sensitization *via* downregulation of dopamine D1 receptor and induction of GPx-1 gene [18]. However, the effect of FIR on activation of cAMP/PKA system and DARPP-32 remains to be determined.

In addition, we and others reported that MA abuse results in mitochondrial dysfunction related to behavioral sensitization [18, 139]. It has been demonstrated that dopamine alters mitochondrial oxidative phosphorylation *via* inhibition of complex 1, finally results in oxidative damage [140, 141]. Moreover, MA-induced mitochondrial dysfunction requires activation of dopamine D1 receptor [142]. We demonstrated that exposure to FIR significantly attenuated intramitochondrial accumulation of Ca^{2+} and decreased mitochondrial membrane potential in response to MA, that positive effects mediated by FIR against MA are comparable to those by D1 receptor antagonist, SCH23390, suggesting that exposure to FIR might recover mitochondrial function *via* inhibition of dopamine D1 receptor and by induction of mitochondrial antioxidant system [18]. Furthermore, FIR exhibit protective effects on a neurodegenerative cell model of spinocerebellar

ataxia type 3 *via* improvement in mitochondrial respiratory function [143]. Taken together, these studies suggested that recovery of mitochondrial function is important for FIR-mediated protective potentials.

2.4. Memory Enhancing Effects of FIR in Response to MA

MA abusers exhibit poorer memory recall than non-users [144]. Additionally, MA abuse leads to the dysfunction of the prefrontal cortex, and causes cognitive impairment [145-147]. Previously, we demonstrated that repeated MA treatment causes memory impairments in mice [125, 148]. Likewise, clinical reports suggested that MA causes cognitive impairment in abusive individuals [149]. Recently, we demonstrated the crucial role of protein kinase C (PKC) in MA-induced memory impairment and oxidative stress [19]. The PKC family consists of 12 isoforms [150, 151], which are further subdivided into three groups according to the regulatory domain and activator domain, *e.g.*, PKCs (cPKCs) α, βI, and βII; novel PKCs (nPKCs) δ, ε, η, and θ; and atypical PKCs (aPKCs) ζ, and λ [152]. In particular, repeated treatment with MA significantly and selectively induces PKCδ, in association with memory impairment [20, 148, 153] In contrast, exposure to FIR attenuates MA-induced phosphorylation of PKCδ, and improves MA-induced memory impairments [20]. Moreover, the memory-enhancing activity by

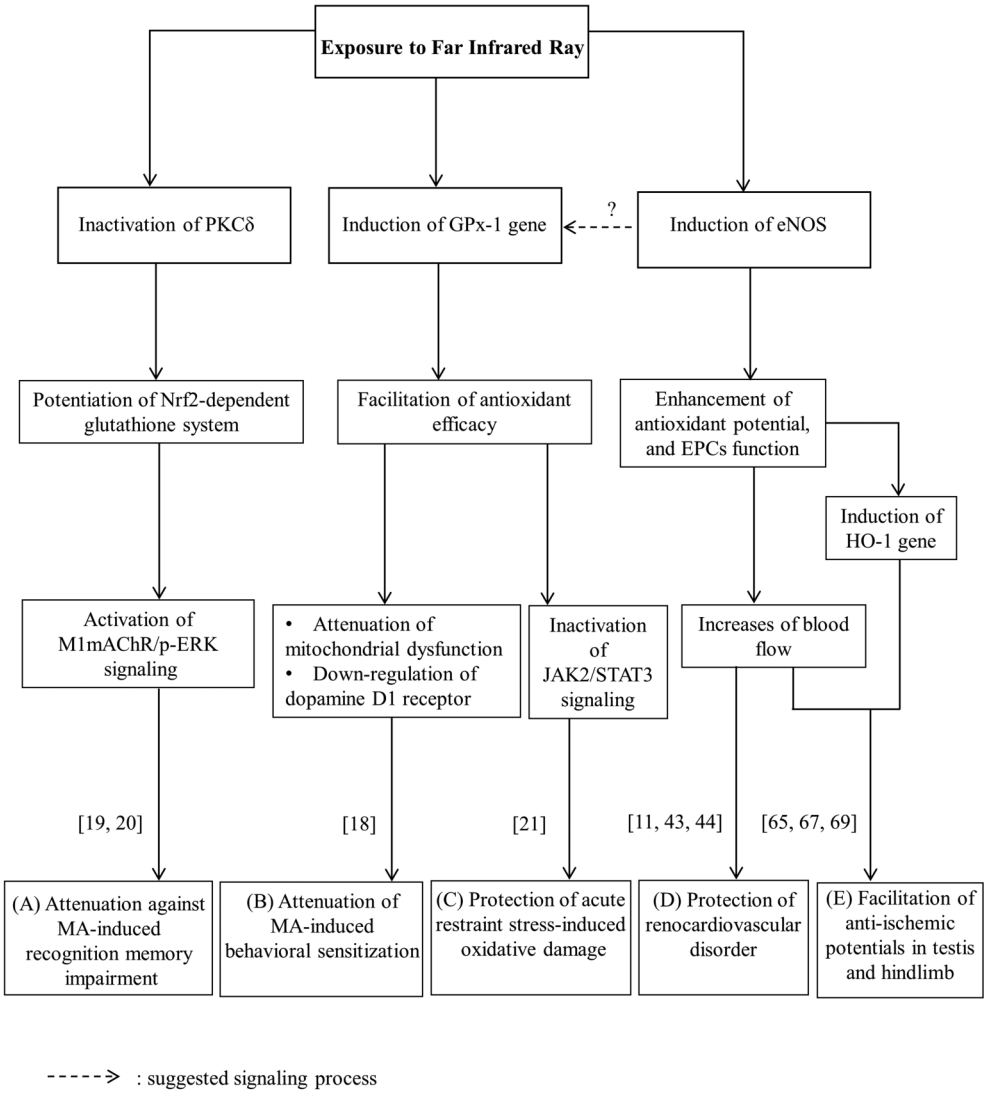

Fig. (1). Schematic depiction on the protective mechanism mediated by FIR. Exposure to FIR inhibits PKC delta, while potentiates Nrf-2-dependent GSH induction, followed by ERK-dependent M1 mAChR up-regulation. The signaling process is important for protecting memory loss induced by MA (**A**). We showed that exposure to FIR enhances antioxidant efficacy *via* induction of GPx-1. This antioxidant potential is helpful for attenuating mitochondrial dysfunction and down-regulation of dopamine D1 receptor, and finally recovery of mitochondrial function and inactivation of D1 receptor are important for protecting behavioral sensitization induced by MA (**B**). In addition, GPx-1-related antioxidant potential attenuates JAK2/STAT3 signaling process. This signaling process is critical for attenuation of acute restraint stress (**C**). Exposure to FIR enhances antioxidant activity and EPCs function *via* induction e-NOS followed by facilitation blood flow, and finally protects from renocardiovascular disorders (**D**). Furthermore, FIR-induced e-NOS stimulates HO-1 level. This mechanism can facilitate anti-ischemic potentials in testis, and hindlimb (**E**).

FIR is comparable to that of genetic depletion of PKCδ [19, 20, 148]. We also found that PKC activator, bryostatin-1, significantly counteracts FIR-mediated memory enhancing effects in response to MA [19]. In addition, it was demonstrated that inhibition of PKCδ modulates eNOS [154, 155] and GSH system [156, 157]. Therefore, it may be speculated that FIR might induce eNOS and GSH, which might be crucial for FIR-mediated memory enhancing potentials [18-20].

MA treatment induced endoplasmic reticulum stress, which might cause depletion of GSH [158, 159], in turn, induce GSH biosynthesis *via* Nrf-2/antioxidant responsive element (ARE) signaling. Nrf2 transcription factor is essential for the induction of c-glutamylcysteine ligase modifier subunit (GCLm), c-glutamylcysteine ligase catalytic subunit (GCLc), GPx, and reduced glutathione (GSH) [160]. Recently, we demonstrated that up-regulation of Nrf2-dependent system might be critical for FIR-mediated antioxidative potential and memory enhancing activity against MA [19].

Muscarinic acetylcholine receptors (mAChRs) are G-protein coupled receptors that consist of five subunits (*i.e.*, M1-M5) [161]. Repeated treatment with MA selectively downregulated M1 mAChR, and resulted in the recognition memory impairment [19]. It was demonstrated that up-regulation of M1 mAChR signaling is essential for memory function in rodents [162, 163]. Consistently, we demonstrated that exposure to FIR protects from MA-induced downregulation of M1 mAChR and associated cognitive dysfunction [19]. Consistently, dicyclomine, a selective M1 mAChR antagonist, counteracted FIR-mediated protective potentials against MA [19]. Moreover, mAChR family activates $ERK_{1/2}$ signaling, which might be responsible for mammalian-associative learning [164, 165], and also might be involved in psychostimulant-induced neuronal plasticity [166, 167]. We reported that MA-induced memory impairment requires downregulation of $ERK_{1/2}$ signaling in prefrontal cortex. In addition, exposure to FIR up-regulates $ERK_{1/2}$ signaling by the interactive modulation between M1 mAChR and Nrf-2 transcription factor, and leads to attenuation against MA-induced memory dysfunction [19]. Consistently, pharmacological inhibitor of ERK, *i.e.*, U0126, counteracted the FIR-mediated effects, suggesting that activation of $ERK_{1/2}$ signaling is crucial for FIR-mediated memory enhancing activity [19]. Interestingly, protective potentials mediated by FIR are comparable to those by clozapine an antipsychotic, and by genetic depletion of PKCδ [19, 20, 125, 148], indicating that FIR can be a potential therapeutic tool in response to MA-induced psychotoxicity.

CONCLUSION

As shown in "1. Preview section", therapeutic potentials of FIR have been well-recognized in diverse pathological conditions. Here, we extended additional findings in this review on the potential therapeutic intervention mediated by FIR. Exposure to FIR ameliorated neuropsychiatric disorders *via* inducing antioxidant-, anti-inflammatory-, antidopaminergic-, and cholinergic-potentials *via* modulating signalings mediated by GPx-1, eNOS, JAK2/STAT3, Nrf-2, PKCδ, dopamine D1 receptor, M1 mAChR, and $ERK_{1/2}$ (Fig. **1** and Graphic abstract).

LIST OF ABBREVIATIONS

AVF	=	Arteriovenous Fistulas
eNOS	=	Endothelial Nitric Oxide Synthase
EPCs	=	Endothelial Progenitor Cells
GPx	=	Glutathione Peroxidase
GSH	=	Reduced Glutathione
HO-1	=	Heme Oxygenase-1
I/R injury	=	Ischemia Reperfusion Injury
IL-6	=	Interleukin-6
JAK2	=	Janus Kinase 2
mAChR	=	Muscarinic Acetylcholine Receptors
N/A	=	Not Available
NO	=	Nitric Oxide
Nrf2	=	Nuclear factor E2-related factor 2
PKC	=	Protein kinase C
STAT3	=	Signal Transducer and Activator of Transcription3
TNF α	=	Tumor Necrosis Factor α

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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