



Incorporating Natural Products, Pharmaceutical Drugs, Self-Care and Digital/Mobile Health Technologies into Molecular-Behavioral Combination Therapies for Chronic Diseases



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Abstract: Merging pharmaceutical and digital (mobile health, mHealth) ingredients to create new therapies for chronic diseases offers unique opportunities for natural products such as omega-3 polyunsaturated fatty acids (n-3 PUFA), curcumin, resveratrol, theanine, or α -lipoic acid. These compounds, when combined with pharmaceutical drugs, show improved efficacy and safety in preclinical and clinical studies of epilepsy, neuropathic pain, osteoarthritis, depression, schizophrenia, diabetes and cancer. Their additional clinical benefits include reducing levels of TNF α and other inflammatory cytokines. We describe how pleiotropic natural products can be developed as bioactive incentives within the network pharmacology together with pharmaceutical drugs and self-care interventions. Since approximately 50% of chronically-ill patients do not take pharmaceutical drugs as prescribed, psychobehavioral incentives may appeal to patients at risk for medication non-adherence. For epilepsy, the incentive-based network therapy comprises anticonvulsant drugs, antiseizure natural products (n-3 PUFA, curcumin or/and resveratrol) coupled with disease-specific behavioral interventions delivered by mobile medical apps. The add-on combination of antiseizure natural products and mHealth supports patient empowerment and intrinsic motivation by having a choice in self-care behaviors. The incentivized therapies offer opportunities: (1) to improve clinical efficacy and safety of existing drugs, (2) to catalyze patient-centered, disease self-management and behavior-changing habits, also improving health-related quality-of-life after reaching remission, and (3) merging copyrighted mHealth software with natural products, thus establishing an intellectual property protection of medical treatments comprising the natural products existing in public domain and currently promoted as dietary supplements. Taken together, clinical research on synergies between existing drugs and pleiotropic natural products, and their integration with self-care, music and mHealth, expands precision/personalized medicine strategies for chronic diseases *via* pharmacological-behavioral combination therapies.



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INTRODUCTION

In addition to search for more effective pharmacological treatments, therapies for chronic diseases have been challenged by medication non-adherence. Due to real-life factors, the complexity of health care delivery, and compromised patient behaviors, this global health care

problem is also being addressed by self-care interventions [1]. Another challenge to improve therapies for chronic diseases is to convert clinically-beneficial natural products into medical treatments due to their public domain status [2]. These two challenges can be simultaneously tackled by overlapping opportunities in digital/mobile medical technologies which can deliver disease self-management content, new intellectual property and patient engagement [3]. This review describes new opportunities to address the aforementioned challenges by combining natural products with pharmaceutical drugs and behavioral interventions. For natural products which improve clinical outcomes, one

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strategy to convert them into medical treatments is by combining them as psychobehavioral incentives together with pharmaceutical drugs and mobile medical software. In the first part, we review clinical and preclinical studies supporting combination therapies consisting of pleiotropic natural products and pharmaceutical drugs. In the second part, we describe medication non-adherence for chronic disorders and premise of using natural products as psychobehavioral incentives to improve therapy outcomes. In the third section, we review evidence for combining antiseizure drugs with natural products and behavioral interventions for the treatment of epilepsy, as an example of incentivized therapy for a chronic disease. Lastly, we provide translational and industry considerations of developing molecular-behavioral combination therapies for chronic medical conditions by merging pharmaceutical and digital ingredients *via* mHealth.

Pleiotropic Natural Products and their Combinations with Pharmaceutical Drugs

Pleiotropic natural products such as omega-3 polyunsaturated fatty acids (n-3 PUFA), α -lipoic acid, curcumin, L-theanine, or trans-resveratrol are extensively tested in clinical trials, while also commonly used as dietary supplements (Fig. 1A) [4-10]. These pleiotropic natural products produce multiple physiological responses through concurrent targeting of various receptors and signaling pathways, and/or scavenging free radicals. Reviews on mechanisms of action for these compounds have been published [11-15]. n-3 PUFA target peroxisome proliferator-

activated receptors (PPARs) and NF κ B transcription factors, selected G-protein coupled receptors, and can also affect cell membrane compositions and metabolic pathways for synthesis of pro-inflammatory eicosanoids [12, 13, 15-17]. α -Lipoic acid mediates antioxidant activity, chelation of metal ions, inhibition of NF κ B and PPARs expression, and modulates lipid and glucose metabolism. Curcumin exerts antioxidant, anticancer and anti-inflammatory activities by targeting redox and inflammatory pathways *via* Nrf2, NF κ B, COX-2, STAT and MAP kinases, as well as cyclin D1, MMP9, VEGF and CXCR4 [5, 11, 14, 18]. Resveratrol can activate α - and β - estrogen receptors, and also modulates diverse antioxidant, apoptotic and inflammatory pathways by activating or inhibiting PPAR α , Nrf2, NF κ B, SIRT1, AMPK, COX1/2 among others [8, 19-23]. These natural products modulate inflammatory cytokines, including TNF α , IL-1 and IL-6 [4, 24-27]. Neuropharmacological effects of theanine are mediated *via* several receptors (GABA(A), NMDA, AMPA, kainite), the nitric oxide pathway, and upregulated expression of brain-derived neurotrophic factor (BDNF) [28-32]. Taken together, pleiotropic natural products can be considered as “a single compound with selective polypharmacology” (Fig. 1B) [33-35].

Clinical studies of the pleiotropic natural products suggest their favorable tolerability, safety and efficacy in several medical indications. n-3 PUFA (omega-3-acid ethyl esters; Lovaza[®] by GlaxoSmithKline) was approved by the US Food and Drug Administration as an adjunct therapy for patients with severe hypertriglyceridemia [36]. Clinical data on metabolism and toxicity of resveratrol suggest that it is

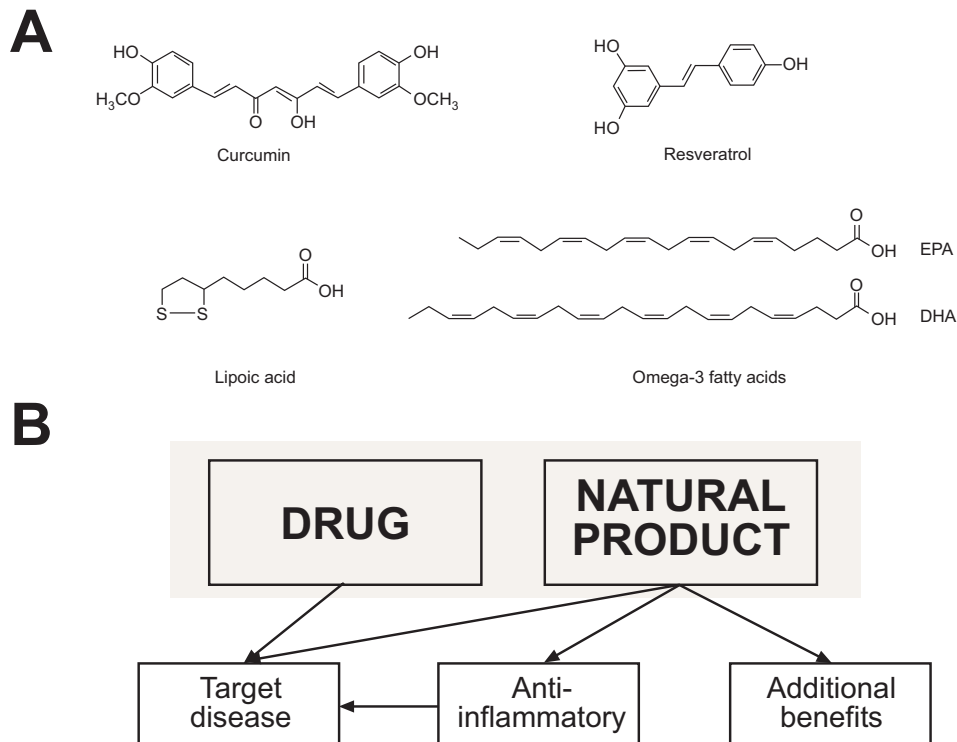


Fig. (1). Structures of selected pleiotropic natural products (A), and their multiple functions within the network pharmacology (B). Pleiotropic natural products exert pharmacological properties *via* specific molecular targets and signaling pathways, while also delivering anti-inflammatory activities. Additional benefits of pleiotropic natural products may include antidepressant, cardiovascular, metabolic, neuroprotective, cognitive, antioxidant, or anticancer activities [11-15, 41].

well tolerated, but clinical efficacy data remain limited [9, 37, 38]. Repeated administration of formulated curcumin (200 mg or 400 mg daily) in cancer patients was safe and well tolerated [39]. Six-week treatments with curcumin (1000 mg/day) appeared safe for patients with major depressive disorders [40]. Safety, tolerability and efficacy of α -lipoic acid was studied in diabetes, Alzheimer's disease (AD), multiple sclerosis (MS), neuropathy and pain [27, 41-45]. Theanine has been clinically tested in patients with schizophrenia [46] and attention-deficit hyperactivity disorder (ADHD) [28]. The pleiotropic natural products are clinically tested as monotherapies or as adjunct therapies to existing medical treatments. Examples of clinical trials showing improved efficacy by combining selected natural products with analgesics, anti-seizure, anticancer, antidiabetic, or antidepressant drugs are shown in Table 1. New opportunities for n-3 PUFA also include cystic fibrosis [47] and asthma [48]. Despite positive effects of the natural products on specific medical conditions (n-3 PUFA in cardiovascular disease (CVD), α -LA for diabetic neuropathy, curcumin in depression), clinical trials of the natural products tested as monotherapies sometimes report inconclusive or negative results. There are also emerging reports which suggest prostate cancer or metabolic risks associated with n-3 PUFA supplementation [49, 50]. Taken together, current clinical results on the natural products suggest their efficacy in therapies in which additional anti-inflammatory and neuroprotective activities are beneficial for a patient.

Preclinical studies on additive and synergistic effects between pharmaceutical drugs and the natural products encourage randomized clinical trials of their combinations as the adjunct therapies [80]. Table 2 summarizes results from studies in animal models of pain, epilepsy, cancer, diabetes and mental disorders. It is important to emphasize that such preclinical animal studies are scarce and, in most cases, their limitations also include a lack of isobolic analysis. Synergistic effects of curcumin with another pleiotropic natural product, epigallocatechin gallate [81, 82], offer new multi-targeted combinations with anticancer drugs [83-85], in addition to their anti-inflammatory activities [24, 86]. From the perspective of combination therapies with curcumin, n-3 PUFA, or resveratrol, pleiotropic natural products were also shown to modulate serotonergic and dopaminergic systems in the brain, thus offering potential for add-on antidepressant or anxiolytic benefits (Table 3). Clinical trials supporting preclinical finding on potential antidepressant benefits are emerging [77, 87, 88]. Since depression is a common comorbidity in epilepsy, pain and other chronic diseases, these additional mood-stabilizing activities may support mental health management during pharmacotherapies. When comparing therapeutic indications between clinical (Table 1) and preclinical (Table 2) studies in combining drugs with natural products, only epilepsy and cancer currently show immediate translational promise. However, in addition to "canonical" challenges when developing new drugs *via* preclinical and clinical studies, additional challenges of incorporating natural products into prescribed medications are having a public domain status

and medication non-adherence (adding "one more pill" may rather discourage a patient, despite clinical benefits).

Medication Adherence as a New Challenge for Treating Chronic Diseases

Approximately 50% of patients with chronic diseases struggle to take medications as prescribed [111], resulting in symptom exacerbation, and increased morbidity and mortality (Fig. 2). Adherence is defined by the World Health Organization as "the extent to which a person's behavior - taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider". Clinical consequences of non-adherence contribute to a decreased quality of life for patients and care givers. Financial consequences of decreased medication adherence include estimated \$100-290 billion per year for the US health care insurance companies and patients [112], as well as revenue losses of \$188 billion per year by the US pharmaceutical industry [113]. Global pharmaceutical industry have an estimated \$564 billion loss per year due to patients' non-adherence [113]. Therefore, improving medication adherence for chronic diseases is a win-win opportunity for patients and health care industry.

Medication adherence is a patient behavioral component of pharmacotherapy. Why does a patient struggle with long-term compliance with taking prescribed medication? For each patient, factors affecting adherence vary, and can be caused by comorbidities (anxiety, stress, depression, fatigue), financial burden, strict medication schedules, miscommunications with doctors, nurses or pharmacists, poor expectations and suboptimal education, or/and limited knowledge and involvement in managing symptoms [122, 123]. Persistence in taking medication can be challenged by drug-related adverse side effects, or by managing a large number of prescription medications [124-126]. Additional reasons are as trivial as forgetfulness and travel, and/or as serious as life style choices and ignorance. Patients with type 1 or 2 diabetes describe fear and embarrassment of injecting insulin as the leading cause of non-compliance [127]. Studies suggest that depression and adverse childhood experiences (ACEs) can be predictors of medication adherence [128-130]. Patient-related factors can be addressed by educating and empowering patients to develop persistence in self-management of pharmacotherapies and disease-related symptoms [3, 131].

INCENTIVIZED THERAPIES

Psychobehavioral Incentives to Improve Medication Adherence

Incentives have been explored as a strategy to improve patient's motivation to comply with his/her pharmacotherapy. This strategy is illustrated in Fig. 3A. Rewarding a patient with incentives is a challenging task, since tangible external rewards can become counterproductive [132]. Financial incentives to reinforce medication adherence face such considerations as ethical, cost-effectiveness and sustainability [133-135]. Incentivizing diabetic patients was recently reviewed in the context of positive perception while

Table 1. Clinical studies showing clinical effects of combining pleiotropic natural products with pharmaceutical drugs.

Indication	Drug	Natural Product	Refs.
ARTHRITIS			
Osteoarthritis pain	NSAIDS	Curcumin	[51]
Knee osteoarthritis	NSAIDS, other analgesics	Curcumin and Glucosamine	[52]
Knee osteoarthritis	NSAIDS	Curcumin	[53]
Knee osteoarthritis	NSAIDS, paracetamol	n-3 PUFA	[54]
Rheumatoid arthritis	Diclofenac sodium	Curcumin	[55]
PAIN			
Burning mouth syndrome	Gabapentin	α -Lipoic acid	[56]
Postoperative pain	Opioid analgesics	Capsaicin	[57]
Chronic neck pain	Superoxide dismutase	α -Lipoic acid	[58]
EPILEPSY			
Drug resistant epilepsy	Antiepileptic drugs	n-3 PUFA	[59]
Drug resistant epilepsy	Antiepileptic drugs	n-3 PUFA	[60]
Refractory seizures	Antiepileptic drugs	n-3 PUFA	[61]
Intractable focal or generalized epilepsy	Antiepileptic drugs	n-3 PUFA	[62]
CANCER			
Pancreatic cancer	Gemcitabine	Curcumin	[63]
Prostate cancer	Docetaxel	Curcumin	[64]
Leukemia	Imatinib	Curcumin	[65]
Breast cancer	Anthracycline-based drugs	n-3 PUFA	[66]
Lung cancer	First-line chemotherapy	n-3 PUFA	[67]
Breast cancer	Paclitaxel	n-3 PUFA	[68]
Prostate cancer	Lycopene	n-3 PUFA	[69]
Gastrointestinal		n-3 PUFA	[70]
DIABETES			
Type 2	Insulin	Resveratrol	[71]
Type 2	Insulin	Curcumin	[72]
Diabetes mellitus and hypertension	Quinapril	α -Lipoic Acid	NCT00795262
Peripheral diabetic neuropathy	Prostaglandin E1	α -Lipoic Acid	[73]
MENTAL DISORDERS			
Depression	Fluoxetine	Curcumin	[40]
	Reserpine (rats)	Curcumin	[74]
Major depressive disorder	Escitalopram	Curcumin	[75]
Major depressive disorder	Selective serotonin reuptake inhibitors (SSRIs)	Creatine	[76]
Depression	Psychotropic drugs	n-3 PUFA	[77]
Schizophrenia	Antipsychotic drugs	Theanine	[78, 79]

Table 2. Preclinical studies showing effects of combining pleiotropic natural products with pharmaceutical drugs.

Medical Condition	Drug	Natural Product	Major Outcome	Refs.
Epilepsy	Valproate	Curcumin	Curcumin enhanced antiseizure activity of subtherapeutic doses of valproate, provide anti-inflammatory and antioxidant effects.	[89]
Epilepsy	Carbamazepine	n-3 PUFA	n-3 PUFA increased protection from seizures in combination with carbamazepine	[90]
Depression	Corticosterone	Curcumin	Curcumin and corticosterone reduces depressive-like behaviors, increased sucrose consumption and reduce mobility time	[91]
Depression	Fluoxetine, Mirtazapine	n-3 PUFA	n-3 PUFA potentiated subtherapeutic doses of antidepressant drugs	[92, 93]
Pain	Morphine	Ginsenosides	Ginsenosides and morphine yielded synergistic antinociception in nociceptive rats	[94]
Pain	Morphine	n-3 PUFA	n-3PUFA potentiated analgesia and prevented tolerance to morphine	[95]
Cancer	Capecitabine	Curcumin	Curcumin potentiated anticancer activity of capecitabine through the NF- κ B pathway	[96]
Cancer	5-Fluorouracil/ Oxaliplatin	Curcumin	Gastric tumor volume was significantly reduced in mice when curcumin was added to a combination of 5-FU/oxiplatin combination.	[97]
Cancer	5-Fluorouracil	Resveratrol	Resveratrol potentiated 5-FU anticancer activity in skin cancer mouse model	[98]
Diabetic Neuropathy	Enalapril	α -Lipoic acid	Enalapril with LA prevented vascular and neuronal damage in diabetic rats	[99]
Ischemic Stroke	Etanercept	α -Lipoic acid	Etanercept with LA enhanced recovery in cerebral infarct, motor deficit and stroke	[100]
Schizophrenia	Clozapine	α -Lipoic acid	Clozapine with LA reversed schizophrenia-like symptoms in mice	[101]

Table 3. Pleiotropic activities of selected natural products studied in humans. Studies and mechanism of enhancing positive mood and activating the brain reward system are also summarized.

Natural Product	Preclinical Data on Antidepressant Activities and Interactions with the Reward System	Refs.
Curcumin	Decreased serum corticosterone levels Increases serotonin by inhibition of monoamine oxidases	[14, 102-105]
	Reduce immobility time and stressed-induced neurodegeneration	[88, 91]
n-3 PUFA	Stabilizes/increases levels of brain serotonin, affects serotonergic transmission	[12]
Resveratrol	Increased serotonin levels in the brain Inhibition of monoamine oxidases (MAO-A)	[106]
L-acetylcarnitine	Enhances dopamine release Upregulation of mGlu2 Receptors	[107-109]
L-Theanine	Increases dopamine levels in the brain Increased levels of BDNF	[110] [31]

decreasing intrinsic motivation by the patients [136, 137]. As alternatives to external incentives, motivational components of mobile and digital technologies for diabetes patients can address the sustainability challenges [138].

Integrating incentives into medical treatment is a new concept in which pharmacological and psychobehavioral elements are combined together into a network therapy

(Figs. 3B and 3C). Such psychobehavioral element is a patient's choice of using (or not using) a pleiotropic natural product and mHealth, thus becoming an empowerment tool for her/his engagement in the therapy. A choice is used as a tool to improve intrinsic motivation [139, 140]. Empowering patients through choices and shared decision-making has been studied [141-144], including epilepsy patients [145].

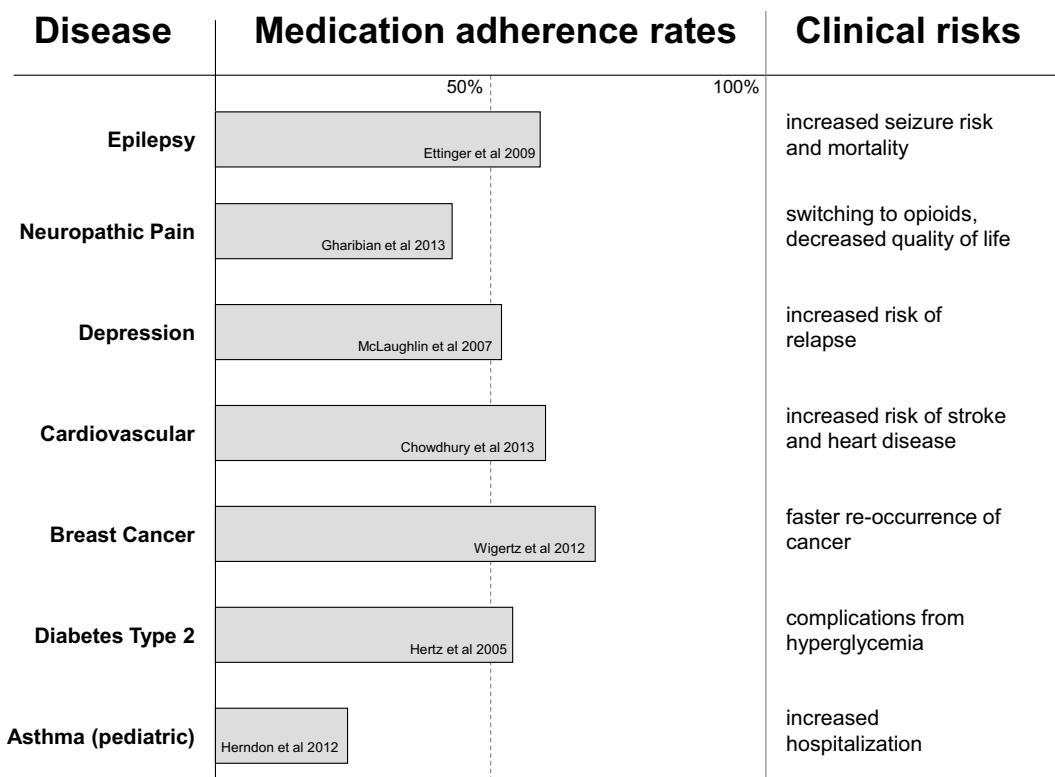


Fig. (2). Medication adherence rates for selected chronic disorders and clinical consequences of non-adherence. Medication adherence values were obtained from medication-possession ratio (MPR) reported in retrospective studies [114-121]. For CVD, a meta-analysis value was used. Adherence data vary significantly in values depending on a population, type of study (prospective or retrospective) and methods used to measure adherence.

Clinical applications of patient empowerment using mHealth technologies were described for cancer, diabetes and other chronic medical indications [146-149]. Disease-specific serious games which incorporate choices and engagement show improved self-management behaviors in patients [150-152].

Integrating psychobehavioral incentives with pharmacotherapies can be presented in the context of network pharmacology (Figs. 1B, 3 and 4), a term usually reserved for describing multi-drug combination therapies and derived from system biology [33, 153]. Development and applications of multi-target, network pharmacology for the treatment of complex chronic diseases has been established for cancer [154, 155], neurotropic pain [156, 157], epilepsy [158], depression [159] and diabetes [160, 161]. Psychological contribution of the placebo effect to pharmacological outcomes has been extensively studied for several chronic medical conditions [162, 163]. Recently, adding psychobehavioral elements to the network pharmacology has been facilitated by disease-specific mobile medical apps [3]. Below, we describe specific examples of how mHealth technologies can further integrate pleiotropic natural products into molecular-behavioral combination therapies.

Incentivized Therapy for Epilepsy

Innovating medical treatments for epilepsy patients is driven by needs to address both the refractory epilepsy and significant medication non-adherence. Approximately 30%

of epilepsy patients are refractory to antiseizure drugs despite taking more than one medication. Consequently this medical condition is subject to non-pharmacological treatments such as the ketogenic diet, vagus nerve stimulation, deep brain stimulation, or brain surgery [164]. Since only 48% of epilepsy patients become seizure-free after taking their first antiseizure drug [165-168], the incentivized therapies may offer better seizure control for newly diagnosed patients. (150,000-200,000 people in the US and approximately 2.4 million people world-wide are diagnosed with epilepsy each year, according to statistics presented by the World Health Organization and the Epilepsy Foundation). Additional challenge for effective treatments for epilepsy patients in prevalence of depression and anxiety as comorbidities [169]. To improve the therapies of pharmaco-resistant epilepsy, medication non-adherence and comorbidities, the drug-device combination therapy consisting of antiseizure medications and a mobile medical app for epilepsy patients was proposed [3]. Herein we describe the incentivized therapy for epilepsy which comprises antiseizure pharmaceutical drugs, antiseizure natural products, and behavioral and self-management components delivered by the mHealth technology. We also review preclinical and clinical evidence for incorporating these elements into the network therapy.

Pleiotropic natural products such as n-3 PUFA, curcumin or resveratrol were shown to exhibit anticonvulsant activities in epilepsy patients as well as in animal models of epilepsy

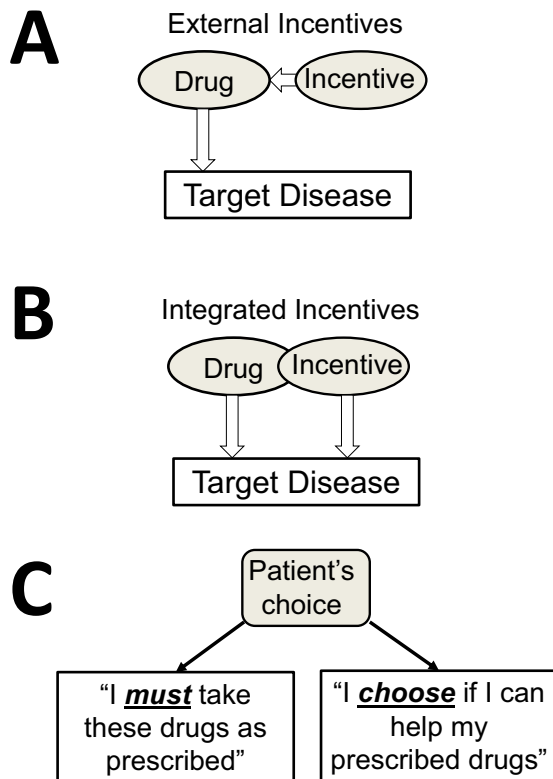


Fig. (3). A psychobehavioral basis of integrating pleiotropic natural product into the network pharmacology in which the compound becomes both an incentive and an active ingredient of the combination therapy. (A) - External incentives are tested to support medication adherence [134]. (B) - A new concept of combining a pharmaceutical drug with a specific natural product which becomes pharmacologically-active incentive. (C) Having a choice as a psychobehavioral incentive targeting an intrinsic motivation of a patient. Shared-decision making and daily self-administration of natural product support self-care.

and status epilepticus. Data from clinical trials suggest that n-3 PUFA may be effective in reducing frequency of seizures in patients with refractory epilepsy [170]. DeGiorgio *et al.* showed in randomized controlled trial (RCT) that a 10-week treatment with fish oil daily dose of 1080 mg DHA/EPA was effective in reducing seizure frequency by 33% in refractory epilepsy adult patients taking 1-4 anticonvulsant drugs [60]. Previous studies with adult epilepsy patients taking fish oil for seizure control were inconclusive [62, 171, 172], however these studies were with higher doses, consistent with the recent finding from the DeGiorgio *et al.* study [60]. The importance of dosing n-3 PUFA in humans and animal studies was previously discussed [173]. In the recent study, pediatric patients with refractory epilepsy were subject to a 3-month treatment with daily fish oil containing 240 mg DHA and 360 mg EPA, resulting in over 50% of patients becoming seizure-free [59]. While these clinical trials were carried out with a small number of patients, the positive results are also supported by preclinical data in animal models of epilepsy [90, 174]. The mechanism by which n-3 PUFA exert their antiepileptic effects is not known although PUFA was shown to affect neuronal excitability in the hippocampus [175, 176] and also

exhibit anti-neuroinflammatory properties [177]. The main PUFA component in the brain is DHA, and some models suggest that n-3 PUFA may modulate neuronal excitability *via* changing levels of sodium-potassium-chloride cotransporters NKCC1 and NKCC2 by affecting lipid rafts through brain cholesterol [178], and shifting conductance of potassium channels [179, 180]. Noteworthy, fatty acids were shown to suppress seizures [181, 182], at least in part due to binding to ionotropic glutamate AMPA receptors [183].

Curcumin and resveratrol exhibit antiseizure activities in animal models of epilepsy. Combinations of curcumin and subtherapeutic doses of antiepileptic drugs (valproate, phenytoin, phenobarbitone and carbamazepine) showed increased protection against seizures in the MES and PTZ models of epilepsy [89]. In the PTZ-kindled mice model of epilepsy, curcumin was effective in a dose-dependent manner attenuating seizure severity and reducing depression-like behavior and memory impairment [184]. In the PTZ-treated rat model of chronic epilepsy, curcumin attenuated cognitive impairment, expression of proinflammatory cytokines in the hippocampus and glial activation [185]. Curcumin also exhibited antiepileptogenic activities in the kainate-induced temporal lobe epilepsy and post-status epilepticus in rats [186-188]. Similar effects were observed for resveratrol in the PTZ-kindled rats [189] and its anti-inflammatory activity *via* the AMPK/mTOR signaling pathway was found in the model of status epilepticus [190]. The use of resveratrol in epilepsy and status epilepticus has been discussed [191, 192]. Potential pharmacokinetic interactions between resveratrol and carbamazepine may prevent this particular combination to treat epileptic seizures [193], similarly to potential interactions between n-3 PUFA and carbamazepine [194].

The mHealth technologies specific for epilepsy patients comprise of mobile medical apps, online resources and wearables intended to help epilepsy self-management, including detecting and monitoring seizures [195-197]. Rapid progress in wireless and mobile EEG interfaces [198, 199] or the EDA-sensors offers unique opportunities for biofeedback-based streaming of digital content developed specifically for epilepsy patients [3]. Examples of online and mobile technologies and apps for epilepsy patients are studied and reviewed [195, 196, 200]. Design features of mobile medical apps intended to reduce frequency of epileptic seizures were previously described [3]. Pharmaceutical industry has been incorporating these new developments, including applications for epilepsy patients. For example, the UCB Pharma partnered with MC10 company in developing the Biostamp, a sensor for detecting seizure movements in epilepsy patients. Among many advances, wearable and mobile app technologies also include the SmartWatch (by Smart Monitor), Embrace (by Empatica), Seizalarm app (Seizalarm) or My Epilepsy (by the Epilepsy Foundation).

Behavioral therapy and self-management for epilepsy patients have been extensively studied and offer self-care strategies to reduce seizure frequency [201-206]. For example, significant reduction of seizures in epilepsy patients was observed during and after six months of psychological and self-management intervention [201]. A randomized trial of behavioral therapy showed a significant

reduction of seizure frequency in older adults with epilepsy [206]. Similar positive results were observed in randomized trial of behavioral interventions in patients with refractory epilepsy [205]. Behavioral-educational interventions were also effective in reducing seizures in children with epilepsy [202]. Clinical efficacy of Mozart's music, including sonata K.448, in reducing seizures in patients with refractory epilepsy [207-209], supports listening to this music for 10 minutes daily as an additional self-care intervention [3]. Mobile medical apps are positioned to reduce and prevent seizures given feasibility and convenience for delivering and monitoring self-care and behavioral interventions. The gamification of mobile medical apps ensure engaging and rewarding content, making patients more eager to engage with their therapies, including medication adherence and disease-related, healthy habits. A recent review emphasizes further needs to study effectiveness of epilepsy self-management strategies [210].

Incentivized therapy for epilepsy incorporating antiseizure pharmaceutical drugs and natural products and self-care delivered by mHealth is illustrated in Fig. 4. The add-on administration of n-3 PUFA (1g or 0.6 g per day for adult or

pediatric patients, respectively), when coupled with mobile medical app, may further improve control of seizures by engaging a patient with the therapy including additional antiseizure natural product and self-care behaviors. Epilepsy-specific behavioral therapy (including awareness of avoiding and managing stress and other seizure-precipitating triggers), educational elements, medication reminders and antiseizure music are provided to the patient *via* mHealth, hence delivering "behavioral" component of the resulting molecular-behavioral combination therapy. The psychobehavioral incentives of having a choice, feeling empowered, and shared-decision making regarding the add-on therapy targets patient intrinsic motivation (Fig. 3B and 3C), further supporting long-term compliance and persistence with the therapy. Epilepsy patients express their desires to be actively involved in choices and shared-decision making [145].

Incorporation of Behavioral Interventions and Self-Care into the Incentivized Therapies for Chronic Diseases

Chronic diseases such as neuropathic pain, epilepsy, cancer, diabetes, CVD, arthritis, asthma, or mental disorders are medical conditions that last at least a year, or are

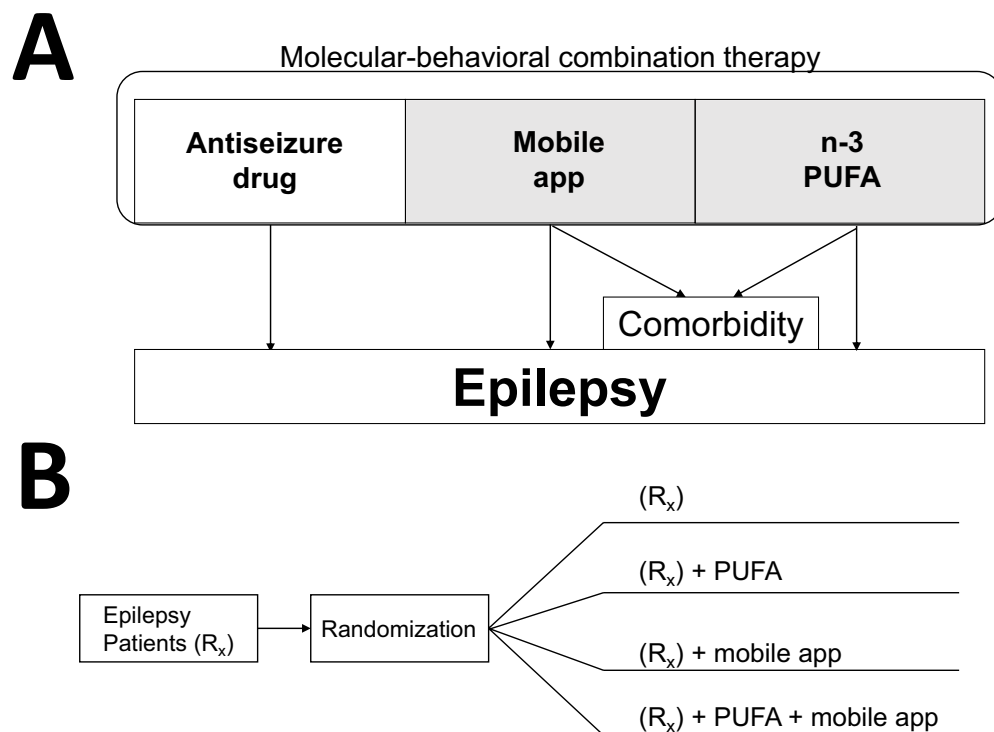


Fig. (4). Molecular-behavioral combination therapy for epilepsy patients. **(A)** Three components of the molecular-behavioral combination therapy are antiseizure pharmaceutical drug, n-3 PUFA as pharmacologically-active incentives, and mobile app delivering antiseizure music and epilepsy self-management content [3]. Given high prevalence of depression as comorbidity for chronic disorders, the add-on therapy (in shaded area) can be specifically prescribed for patients with refractory epilepsy and experiencing symptoms of depression. Mobile apps and software for treating depression and anxiety show promise in clinical trials [211-213]. In addition to n-3 PUFA, curcumin also can be developed as psychobehavioral incentives due to its antiseizure and antidepressant activities. **(B)** An example of a parallel study design to test the molecular-behavioral combination therapy in form of a drug-device combination product. Patients with refractory epilepsy are usually given two or more antiseizure drugs (R_x group). To establish efficacy of all possible combinations, such four-arm study can last 6-12 months, and can further include crossover, as was previously used to establish efficacy of n-3 PUFA in patients with refractory epilepsy [60], or/and a delayed start/prerandomization to reduce placebo responses [214]. Determining pharmacokinetic interactions between natural products and antiseizure drugs are important to ensure the safety of the drug-drug combination study (2nd and 4th arm), even though natural products may have prescription medicine status (e.g. n-3 PUFA as Lovaza[®] or Vascepa[®]).

permanent. Because of the long duration, chronic medical conditions challenge patients, caregivers and healthcare systems, and also pose a major economic burden [215, 216]. An additional challenge for managing a chronic disease happens after achieving remission and discontinuation of pharmacotherapies. The Center for Disease Control and Prevention (CDC) emphasized importance of behavioral components (such as physical activity, nutrition) which can prevent progression of chronic diseases [217]. Supporting healthy habits during the therapy and also after reaching remission (during the inactive-disease state) is critical for long-term improvements in therapy outcomes and health-related quality of life.

Patient self-care and disease self-management become important behavioral components of patient-centered health care [218, 219]. Self-care can be considered as a combination of disease self-management and self-efficacy, where self-management can be described as patient's skills and behaviors affecting disease symptoms, and self-efficacy is patient's motivation and perceived ability to engage in self-management behaviors. The relationship between self-management and self-efficacy is shown in Fig. 5A. Incorporation of disease-specific behavioral and self-care components into patient daily life has been facilitated using mHealth technologies. For example, listening to the antiseizure music and avoiding seizure-triggers are daily behavioral components to help epilepsy patients to reduce and prevent seizures. There is accumulating clinical evidence for other non-pharmacological, behavioral interventions for specific chronic medical conditions. Therapeutic physical exercise was validated for rheumatoid arthritis (RA) [220, 221], major depressive disorder [222], neurodegenerative disorders [223], neuropathic pain [224], pediatric cancer [225], or perioperative management, postoperative recovery and outcomes [226]. Physical exercise programs for patients with RA may additionally improve their health-related quality of life by improving sleep and fatigue [227]. Yoga improved disease-symptoms for patients with low-back pain [228-230], cancer-related fatigue [231, 232], osteoarthritis [233-235], epilepsy [236], asthma [237], diabetes [238] and PTSD [239]. Music-supported therapies include medical indications such as pain, epilepsy, stroke, myocardial infarct, dementia, depression, anxiety, and other psychiatric disorders (references in [3] and [240-242]). The pleiotropic nature of music is mediated by neurochemical changes in the brain, endocrinological and immune systems [243-245], activating the mesolimbic system and dopaminergic neurotransmission [246-251]. Recent studies suggest that exposure to Mozart and Bach music can upregulate brain-derived neurotrophic factor (BDNF) [252, 253]. Nutrition-based interventions have shown clinical efficacy in reducing seizures in epilepsy patients [254-256], but more studies on pharmacokinetic interactions with antiepileptic drugs are needed [257, 258]. Nutrition has been effective non-pharmacological treatment for CVD [259], diabetes [260], or arthritis including combinations with physical exercise [261]. Taken together, cognitive behavioral therapy, music, nutrition, physical exercise and yoga are already being combined into behavioral interventions and self-care using mHealth [262-264].

Self-administration of an optional (add-on) treatment targets patient intrinsic motivation, and can promote long-

lasting behavioral changes by engaging habit-forming mechanisms [265, 266]. As illustrated in Fig. 5B, an opportunity to self-administer the clinically-efficacious dose of the pleiotropic natural product and other self-care behaviors, leads to activating the reward system and creating a habit-forming loop. Engaging habit-forming neuronal networks in the brain may facilitate health-promoting behavioral benefits [267, 268]. mHealth and gamification principles offer additional tools to engage, monitor and virtually reward a patient [269-271]. While self-administration of pleiotropic natural products can improve pharmacotherapy outcomes, it is nonpharmacological treatments that hold long-term potential for introducing new healthy routines in chronically-ill patients. This aspect becomes critical once a chronically-ill patient reaches a stage of clinical remission and inactive disease state, since she/he is in a vulnerable state due to behavioral and life-style contribution to the disease and the therapy outcomes. Additional benefit of incorporating clinically-efficacious behavioral interventions is the opportunity to reduce dosing of pharmaceutical-based therapies (Fig. 5C). While this application is apparent for patients with neuropathic pain being treated with opioids, or arthritis patients taking NSAIDs and other anti-inflammatory medications, future clinical studies will evaluate its potential use in treating epilepsy, depression, cardiovascular and other chronic medical conditions [4, 5, 21, 25, 60, 191, 192].

Industry and Translational Considerations

This article describes the use of pleiotropic natural products in combinations with existing pharmaceutical drugs and self-care delivered by the mHealth technology. From the regulatory point of view, this is a multifaceted challenge, requiring judicious and cooperative endeavor to develop such integrated medical treatments. Incorporating natural product or self-care delivered by mHealth already creates numerous challenges, and integrating two or more modalities is even more difficult. Clinical development of drug-device combinations can be facilitated by a natural product having the status of prescribed medication, or/and mobile app reaching the status of regulated medical device.

For patients, many natural products are currently available as supplements, for which health claims and benefits are regulated by federal agencies [272]. Because dietary supplements market is becoming increasingly competitive due to fast growth, there are new tensions and opportunities to innovate these products. Converting natural products from dietary supplements into regulated medical treatments requires clinical studies on optimizing dosing, duration and drug-drug interactions to achieve maximum efficacy and safety for each specific medical indication. However, the lack of intellectual property protection of natural products is a challenge for developing them as medical treatments. A problem of patenting natural products was previously exemplified with curcumin [273, 274], whereas patenting guidelines also change for newly-discovered natural products [2]. Improving bioavailability of curcumin [275, 276], or generating derivatives of resveratrol [277, 278] are viable patenting strategies to improve their efficacy. To this end, combining natural products with disease-specific behavioral interventions *via* mHealth offers

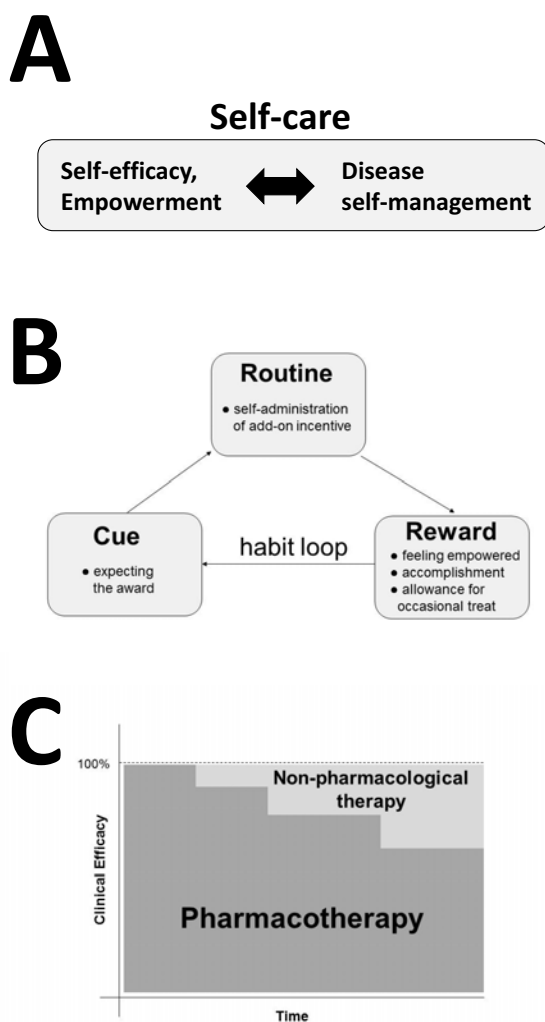


Fig. (5). Roles of self-care and the reward system in the incentivized therapies. Due to the long duration of chronic medical conditions, healthy habits and self-care can slow down progression of the chronic disease, improve the therapy outcomes and the health-related quality of life after reaching remission. **(A)** Self-care consists of disease self-management (patient behaviors related to management and prevention of disease symptoms), self-efficacy and empowerment (perceived abilities to cope with, control and manage disease symptoms). Digital technologies become effective means to deliver empowerment and disease self-management content [148, 150]. **(B)** Patients activate the habit-forming mechanism by a self-administration of an incentive. The habit-forming loop scheme is adapted from “*The Power of Habit*” by Charles Duhigg. **(C)** Integration of incentive-based nonpharmacological interventions with pharmacotherapies can lead to decreasing the dose of pharmaceutical drugs, an opportunity instantly applicable in the treatment of chronic, neuropathic pain with opioids, or arthritis with NSAIDs and other anti-inflammatory drugs. Randomized clinical trials will determine if this strategy also applies to epilepsy patients or those with depression to decrease dosing or number of medications.

an additional level of intellectual property protection by merging copyrights (lasting over 50 years) with a pharmacologically-active compound which exists in public domain [3]. This strategy creates new regulatory challenges

and requires closely working with the regulatory agencies to ensure the safety of patients and following proper regulatory mechanisms. Additional benefits of the regulatory pathway for developing natural products in combinations with mHealth include new strategies to innovate and validate new medical interventions, instead of following costly litigations (e.g. the 2015 Vascepa[®] case related to off-label claims).

Converting mobile apps into a regulated medical device requires pivotal clinical trials in support of regulatory clearance [279, 280]. Current regulatory guidelines indicate that apps delivering disease self-management content are likely exempt from premarket approval, subject to the discretion of the regulatory agencies. For combinations of mobile apps with natural products, their intended use for specific medical condition, marketing, and labelling must be supported by appropriate clinical studies, and subject to premarket notification or approval. A mobile app for tracking the use of dietary supplements, MyDS, was developed by the National Institute of Health Office for Dietary Supplements (the app was discontinued in June 2015) [281]. Regulatory challenges and growth of mHealth have resulted in excessive number of health-related and wellness apps, creating a problem of credibility and confusion [282], thus also creating opportunities for digital technologies to be part of clinically-validated integrative medicine [283]. The mHealth technology is becoming a part of personalized medicine [284], and several companies have been pioneering development of mobile medical apps and games as medical treatments. Health care providers support incorporation of mHealth into primary care practice and reimbursement policies [285].

Given multiple components of the incentivized therapy, the discovery and characterization of synergistic effects among natural products, pharmaceutical drugs and mobile medical apps is challenging at both preclinical and clinical levels. At a preclinical level, it is important to test combinations of natural products and pharmaceutical drugs using isobolic analysis, or sub-effective therapeutic doses. At a clinical level, large-scale, controlled testing is challenging due to additional placebo-related responses, driven by spontaneous remissions, methodological bias and psychobiological mechanisms of positive expectations and learning [162, 163, 214, 286]. The neurobiological mechanisms of the placebo effect are mediated by specific neurotransmitters, including dopamine, neuropeptides and their receptors located in different brain structures [162, 163]. To this end, the expectation-driven placebo effect may overlap with music and therapeutic games due to activating dopaminergic signaling in the patient’s reward system [3]. One possible mechanism of such additional placebo-like effects is that music and judiciously-timed digital images can produce temporal expectations [287-290]. To best of our knowledge, the synergistic effects between pharmacological and non-pharmacological treatments have not been demonstrated.

Optimal design of randomized and placebo-controlled clinical trials for any new therapy is critical for demonstrating its efficacy [291]. Even for testing monotherapies, there are challenges to account for placebo effects and responses that are often disease-specific and interwoven with natural fluctuations of chronic disease symptoms. In the case of

epilepsy, the placebo effects and responses were observed for both antiseizure drugs and medical devices, and several study designs have been proposed to mitigate placebos [214], including adjusting “time to prerandomization” [292], or “delay start” [293]. Clinical testing of combinations of antiseizure drugs with natural products (n-3 PUFA) was accomplished using randomized and placebo-controlled crossover design with three periods in which patients with refractory epilepsy were receiving low- or high-dose of n-3 PUFA or placebo while taking their antiseizure medications [60]. Testing more complex combination therapies, such as those containing pharmaceutical drugs, natural products and mobile medical apps (*e.g.* shown in Fig. 4A) will require judicious design of parallel and randomized trials to account for placebo and nocebo effects, likely adding additional challenges associated with multiple testing sites. In addition to universal ethical aspects of reducing or enhancing the placebo effects in patients during the treatment of a chronic disease, additional ethical aspect of including the placebo arm in epilepsy patients is the increase of SUDEP (sudden unexplained death in epilepsy) [294].

From a translational perspective, the long-term premise of developing the combinations of pharmaceutical drugs, natural products and self-care is the creation of the molecular-behavioral combination therapies in which seamless integration of behavioral and pharmaceutical interventions is delivered. As illustrated in Fig. 4, the molecular-behavioral combination therapy for patients with epilepsy can consist of the antiseizure drug, n-3 PUFA and behavioral, self-management content (like listening to antiseizure music, avoiding seizure-triggers). Such strategy is also favorable for patients with neurological disorders in which inflammatory and behavioral components significantly contribute to disease symptoms. Large-scale, randomized and controlled clinical studies on interactions between behavioral and pharmacological interventions will shed more light on mutual relationships, yielding new rational strategies for personalized, precision and preventive medicine [295-297]. Translational perspectives for developing broad-spectrum approach and integrative therapies are discussed for mental disorders [298, 299] and cancer [80]. Better understanding of interactions between natural products and drug targets, and mechanisms by which enriched environment (nutrition, physical exercise), cell metabolism and epigenetics may affect pharmacological properties of drug candidates [300, 301], will facilitate design of incentivized therapies combining the most effective components.

CONCLUSION

Pleiotropic natural products or nonpharmacological treatments can be incorporated into pharmacotherapies as psychobehavioral incentives to improve therapy outcomes for chronically-ill patients. Such integrative approach results in molecular-behavioral combination therapies, possible to deliver by digital medical technologies. There is an apparent need for controlled clinical trials to account for the placebo responses and to validate the effectiveness of these pharmacological and non-pharmacological combinations. Incentivized medical treatments offer an opportunity to improve medication adherence and clinical efficacy of existing pharmaceutical drugs. In addition, the ability to

catalyze habit-changing healthy behaviors in patients favors improvements in the health-related quality of life during pharmacotherapy and after reaching remission. This aspect offers unique opportunities to bridge symptomatic treatments with preventive medicine, and has implications for public health by addressing risk factors and burden of chronic diseases [302, 303]. Lastly, once the drug-device combination product is approved by a regulatory agency, merging copyrights of mHealth software with natural products will afford new proprietary products containing natural products currently existing in public domain. Engaging patients with their therapies using mHealth-delivered behavioral interventions will improve their experience with medical treatment. Taken together, combining the clinical efficacy of natural products and pharmaceutical-based treatments with self-care will advance patient-centered health care.

ABBREVIATIONS

BDNF	=	brain-derived neurotropic factor
CVD	=	cardiovascular disease
DHA	=	docosahexanoic acid
EDA	=	electrodermal activity
EEG	=	electroencephalograph
EPA	=	eicosapentaenoic acid
5-FU	=	5-fluorouracil
LA	=	α -lipoic acid
MES	=	maximum electroshock
mHealth	=	mobile health technologies
MPR	=	medication possession ratio
NSAIDs	=	nonsteroidal anti-inflammatory drugs
PPARs	=	peroxisome proliferator-activated receptors
PTZ	=	pentylentetrazol
n-3 PUFA	=	omega-3 polyunsaturated fatty acids
RCT	=	randomized controlled trial

CONFLICT OF INTEREST

GB is a cofounder of Epicadence PBC, Public Benefit Corporation, a company developing mobile software as medical devices for treating chronic medical conditions.

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