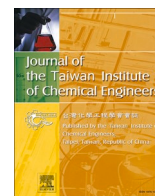




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# Interactive deciphering electron-shuttling characteristics of agricultural wastes with potential bioenergy-steered anti-COVID-19 activity via microbial fuel cells

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## ABSTRACT

**Background:** This first-attempt study explored indigenous herbs from agricultural waste with bioenergy and biorefinery-stimulating potentials for possible anti-COVID-19 drug development. As prior novel study revealed, medicinal herbs abundant in *ortho*-dihydroxyl substituents and flavonoid-bearing chemicals were likely not only electron shuttle (ES)-steered, but also virus transmission-resisted.

**Methods:** Herbal extract preparation from agricultural wastes were implemented via traditional Chinese medicine (TCM) decoction pot. After filtration and evaporation, a crude extract obtained was used for evaluation of bioenergy-stimulating and electron-mediating characteristics via microbial fuel cells (MFCs). Combined with cyclic voltammetric analysis, MFCs provided a novel platform to distinguish electron shuttles from antioxidants with electron-transfer steered antiviral potentials of herbal extracts.

**Significant findings:** After 50 serial cyclic voltammogram traces, considerable ES activities of herbal extracts still stably remained, indicating that possible medication-associated capabilities could be persistent. This work also extended to explore bioenergy-stimulating herbs from agricultural waste recycling for bioenergy and biorefinery applications. Water extract of *Coffea arabica* was more biotoxic than ethanolic extract, resulting in its lower power-generating capability. The findings revealed that water extract of *Trichodesma khasianum* and *Euphorbia hirta* could exhibit considerable bioenergy-enhancing effects. For cradle-to-cradle circular economy, agricultural waste could be specifically screened for possible regeneration of value-added anti-COVID-19 drugs via bioenergy selection.

## Nomenclature

Sample abbreviation	Plant (part)	Solvent of extraction
VPL-H <sub>2</sub> O	<i>Vanilla planifolia</i> (leaves)	water
VPL-95E		95% EtOH
VPP-H <sub>2</sub> O	<i>Vanilla planifolia</i> (pods)	water
VPP-95E		95% EtOH
VPS-H <sub>2</sub> O	<i>Vanilla planifolia</i> (stems)	water
VPS-95E		95% EtOH
LCL-H <sub>2</sub> O	<i>Litchi chinensis</i> (leaves)	water
LCL-95E		95% EtOH
LCS-H <sub>2</sub> O	<i>Litchi chinensis</i> (stems)	water
LCS-95E		95% EtOH
CA-H <sub>2</sub> O	<i>Coffea arabica</i> (leaves)	water
CA-95E		95% EtOH

(continued on next column)

(continued)

Sample abbreviation	Plant (part)	Solvent of extraction
VA-50E	<i>Vigna angularis</i> (seeds)	50% EtOH
VA-95E		95% EtOH
VR-50E	<i>Vigna radiata</i> (seeds)	50% EtOH
VR-95E		95% EtOH
GM-50E	<i>Glycine max</i> (seeds)	50% EtOH
GM-95E		95% EtOH
MI-H <sub>2</sub> O	<i>Mangifera indica</i> (peels)	water
BC-H <sub>2</sub> O	<i>Bombax ceiba</i> (flowers)	water
TK-H <sub>2</sub> O	<i>Trichodesma khasianum</i> (leaves)	water
TT-H <sub>2</sub> O	<i>Euphorbia hirta</i> (aerial parts)	water
AH-H <sub>2</sub> O	<i>Artocarpus heterophyllus</i> (seeds)	water
AG-H <sub>2</sub> O	<i>Asystasia gangetica</i> (aerial parts)	water

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## 1. Introduction

For exploration of green sustainable biomass energy, microbial fuel cells (MFCs) are popularly used as one of bioelectrochemical devices that govern electric currents obtained from organics utilization through electroactive microbes [1]. To improve bioelectricity-generating capabilities via effective reduction of mass transfer resistance of intra-phases (e.g., biofilm-and-electrode, biofilm-and-culture broth resistances), exogenous supplement of environmentally-friendly electron shuttles (ESs or redox mediators) to considerably stimulate bioenergy extraction was found to be economically promising [2–4]. Moreover, supplement of natural ESs would be more bio-electrochemically applicable and ecologically appropriate to desperately eliminate negative impacts to the environment. In fact, the chemicals bearing at least two electrophilic substituents (e.g., hydroxyl (-OH) and/or amino (-NH<sub>2</sub>) functional groups) on benzene ring *ortho* or *para* to each other would be energetically display redox-mediating characteristics as ESs [5–8]. Furthermore, as electrochemical analysis (e.g., cyclic voltammetric evaluation) illustrated, hydroxyl substituent(s) would be more electrochemically-stable and energetically-reversible to persist favorable electron-shuttling potentials for bioenergy expression. For instance, chemicals bearing hydroquinone-associated chemical structures as ESs own encouraging efficiency to stimulate electron transport phenomena. Thus, according to MFCs as a platform of evaluation, apparently polyphenolics-abundant natural bioresources (e.g., herbal medicines and edible crops and vegetables) would be more biocompatible for further electrochemically promising bioenergy applications. Due to aforementioned reason, Chen et al. [9,10] referred to Compendium of Materia Medica (Běncào gāngmù) to select more than 20 so-called “energy-abundant” or refreshing herbal species to scrutinize their electron transfer (ET)-mediating practicability. The results directly revealed that *Camellia* green tea, *Syzygium aromatum*, *Circus reticulata*, *Lonicera japonica* are strongly electrochemically associated. These medicinal herbs could significantly maintain electrochemically reversible and stable activity (e.g., redox potentials of ESs) for bioenergy extraction. In fact, due to this bioenergy-activating potentials, new perspectives of ET-catalyzed disease treatment were thus disclosed for drug development. Moreover, for consideration of “bioenergy medicine”, such innovative findings also first-time distinguished ESs from the category of polyphenol antioxidants due to their persistent and electrochemical catalysis. Owing to these novel findings of medicinal herbs, Chen et al. [10] concluded that *ortho* and *para* dihydroxyl substituents-bearing on the benzene ring of chemicals should own prerequisite potential for pharmacological applications (e.g., antiviral treatment). As a matter of fact, follow-up studies confirmed that *ortho*-dihydroxyl group (*o*-diOH)-carrying neurotransmitters (i.e., levodopa (L-DOPA), dopamine) were of great significance to treat cranial nerves-associated disease (e.g., Parkinson’s disease (PD) and Huntington’s disease (HD)). These all pointed out that promising electron-shuttling capabilities of medicines, *o*-diOH bearing epinephrine and norepinephrine should play some crucial role to disease treatment. In fact, serial studies suggested that above-mentioned crucial medicines could be keystone intermediates to surmount blood-brain barrier for functions of central nervous system. These work exhibited that ET-stimulating characteristics coupled with bioenergy-steered capabilities might be linear treatment-manipulating to alleviate neurological disease. Moreover, multiple hydroxyl groups-bearing chemical species (e.g., gallic acid, theaflavin, epigallocatechin gallate (EGCG)) of *Camellia* green tea were even found to have cancer preventive and therapeutic effects (e.g., synergistic inhibition of cancer growth). It was thus noticed that chemical species containing both *ortho*-dihydroxyl groups and flavonoid might synergistically trigger encouraging antiviral characteristics to treat severe acute respiratory syndrome (SARS), severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) (i.e., COVID-19), Middle East respiratory syndrome coronavirus (MERS-CoV), dengue fever and so forth. Due to the COVID-19 pandemics, prior first-attempt screening

upon commonly-used herbal species of COVID-19 traditional Chinese medicine (TCM) strongly confirmed that bioenergy-steered and ET-stimulating characteristics were of great significance to efficacious antiviral activities, in particular anti-COVID-19 capabilities [11]. Thus, considering circular economy with worldwide aspects of bioenergy and biorefinery, agricultural waste as a potential value-added biomaterial should also contain diverse phytochemical constituents for antiviral applications. As known, phytochemicals can at least be divided into alkaloid, saponin, flavonoid, lignan, anthraquinone, phenylpropanoid, coumarin, glycoside and others [12–16]. Flavonoid is one of secondary metabolites polyphenol natural products. Recent literature showed that flavonoid has miscellaneous pharmacological activities (e.g., antioxidant, anti-inflammatory, anticancer and chronic disease attenuation). Especially, the inhibition by target organ(s) of coronaviruses SARS, MERS and COVID-19 has been reported [17]. Since the application of anti-COVID-19 using traditional Chinese medicine (TCM) for therapy or prevention was recently mentioned, pharmacological activity generally targets to clear heat and resolve toxin, benefiting qi and nourishing blood, moistening lung for removing phlegm [18]. The TCM also contained the major flavonoids such as quercetin, kaempferol and baicalein. As a matter of fact, such chemicals bearing dihydroxyl groups on the benzene ring could also possibly reveal electrochemically promising ET-stimulating characteristics. Moreover, these flavonoids have been explored on their network pharmacological properties for anti-COVID-19 treatment [19]. Thus, this work extended such core perspectives to postulate that agricultural wastes of traditional and folk medicine possibly dealing with anti-viral or COVID-19 medication should be strongly related to ET-oriented characteristics for green-sustainable bioresource recycling. Chiefly, as literatures mentioned, Taiwan’s agricultural waste was ca. 4.6 million tons from 2001 to 2019, most of agricultural wastes (ca. 93.5%) could be applied to *in-situ* tillage, burying and composting or other applications [20]. Considering cradle to cradle material recycling, this feasibility study selected indigenous folkloric medicinal plants (most of them are agricultural waste) with such phytonutrient properties in Taiwan. Moreover, this feasibility study tended to clarify whether water or ethanol extracts of polyphenols and/or flavonoids-abundant plants may also have considerable capabilities of not only potentials of herbal medicines, but also characteristics of biomass energy and bio-refinery (Table 1) [21–35].

Therefore, this first attempt study specifically selected the root, stem, leaf portion of ca. 12 herbal species of bioenergy abundant folklore medicine or habitual food sources to obtain water and/or ethanol extracts for bioenergy-stimulating assessment. This work also considered ecological integrity to conserve Taiwan’s indigenous medicinal herbs, revealing that ET-steered and bioenergy-stimulating features are associated with pharmacological and medicinal potentials (e.g., antiviral activities). Apparently, this study concluded that *Trichodesma khasianum* clarke (Jiǎ Suān Jiāng yè) and *Euphorbia hirta* L. (Fēi Yáng Cǎo) were of considerable bioenergy potentials for antiviral activities. This study provided a plausible rationale to screen upon practicable herbs and/or agricultural waste for COVID-19 drug development.

## 2. Materials and methods

### 2.1. Plant extracts preparation

*Vanilla planifolia* leaves, pods and stems, *Litchi chinensis* leaves and stems, *Mangifera indica* peels, *Bombax ceiba* flowers and *Asystasia gangetica* were collected from Orchid Cultivation and Teaching Greenhouse, Lychee Garden and Mango Garden of Chang Jung Christian University, Tainan City, Taiwan. *Vigna angularis* (seeds), *Vigna radiata* (seeds) and *Glycine max* (seeds) were purchased from Traditional Chinese Medicine store in Tainan City, Taiwan. *Euphorbia hirta* and *Artocarpus heterophyllus* (seeds) were provided by Dr. Ko, Shun-Yao from Chang Jung Christian University, Tainan City, Taiwan. *Coffea arabica*

**Table 1**

Comparative list of the traditional and folkloric medicinal plants with phytochemical components selected in this study.

Plant/part	Solvent of extraction	Contents of secondary metabolites	Refs.
<i>Artocarpus heterophyllus</i> seeds	water	Phenolic, flavonoid content	[21]
<i>Asystasia gangetica</i> aerial parts	water	Polyphenol, flavonoids, condensed tannin, polysaccharides	[22]
<i>Bombax ceiba</i> flowers	water	Alkaloids, flavonoids, glycosides, coumarins, proteins and amino acids.	[23]
<i>Coffea arabica</i> leaves	water	Catechin, epicatechin, mangiferin, isomangiferin, procyanidin B, caffeoylquinic acids (CQA), caffeine, quercetin-3-O-glucoside, procyanidin C, rutin, 3,4-diCQA.	[24]
<i>Euphorbia hirta</i> aerial parts	95% EtOH water	Ellagic acid derivatives, ellagitann, gallotannin, flavonols, hydroxycinnamic acids, hydroxybenzoic acids.	[25]
<i>Glycine max</i> seeds	50% EtOH 95% EtOH	Hydroxycinnamic acid derivatives, flavonol derivatives, isoflavone derivatives, rutin, daidzin, daidzein, genistein.	[26]
<i>Litchi chinensis</i> leaves	water 95% EtOH	Flavan-3-ols, proanthocyanidins, sesquipinsapol B, sesquimarocanol B	[27]
<i>Litchi chinensis</i> stems	water 95% EtOH	Polyphenol	[28]
<i>Mangifera indica</i> peels	water	<i>p</i> -Hydroxybenzoic acid, gallic acid, pyrogallol, chlorogenic acid, catechin gallate, <i>p</i> -Coumaric acid, epicatechin gallate	[29]
<i>Trichodesma khasianum</i> leaves	water	Polyphenol, rosmarinic acid	[30]
<i>Vigna angularis</i> seeds	50% EtOH	Vitexin, isovitexin, polyphenol, flavonoids, condensed tannin, saponin	[31, 32]
<i>Vigna radiata</i> seeds	95% EtOH 50% EtOH 95% EtOH		
<i>Vanilla planifolia</i> leaves	water	bis[4-( $\beta$ -D-glucopyranosyloxy)-benzyl]-2-isopropyltartrate (glucoside A), bis[4-( $\beta$ -D-glucopyranosyloxy)-benzyl]-2-(2-butyl)tartrate (glucoside B), sucrose, $\alpha$ -glucose, $\beta$ -glucose, malic acid, homocitric acid, acetic acid.	[33]
<i>Vanilla planifolia</i> pods	95% EtOH water	vanillic acid, ethyl vanillin, 4-hydroxybenzyl alcohol, 3,4-dihydroxybenzaldehyde, 4-hydroxybenzoic acid, 4-hydroxybenzaldehyde, vanillyl alcohol, <i>p</i> -coumaric acid, Coumarin, ferulic acid, piperonal, glucovanillin, <i>p</i> -cresol, creosol, bis[4-( $\beta$ -d-glucopyranosyloxy)-benzyl]-2-isopropyltartrate and bis[4-( $\beta$ -d-glucopyranosyloxy)-benzyl]-2-(2-butyl) tartrate	[34]
<i>Vanilla planifolia</i> stems	95% EtOH water 95% EtOH	Vanilla glucoside, vanillin, 4-hydroxybenzaldehyde, 4-hydroxy benzyl alcohol, vanillic acid, ferulic acid	[35]

(leaves) and *Trichodesma khasianum* (leaves) were collected from Pingtung City, Taiwan.

Plant materials were first dried in an enclosed oven maintained at 40°C for 3 days. Then, the samples were powdered to significant reduction of particle sizes by osterizer blender. Approx. 50 g herbal powder blends were used for extraction in 1:20 ratio with deionized water boiling. The decoction with water was employed in traditional Chinese decoction pot until the water volume was decreased to ca. 200 mL. The residual liquid of crude extracts was removed using rotary evaporator. Following aforementioned preparation of powdered materials, herbal powder blends were sampled for extraction in 20 fold volume of 50% ethanol and 95% ethanol at 65°C water bath incubator under 2 h reflux. The residual liquid of the resultant extracts were then removed using rotary evaporator. Finally, the harvested extracts were frozen-dried to remove solvent residues via vacuum operation.

## 2.2. Cyclic voltammetry (CV)

To assess the electrochemical performance of herbal extract, CV scanning of these candidate extracts for 50 cycles was carried out through electrochemical workstation (ALS/DY2325 BI-POTENTIOSTAT, Taiwan). For three-electrode system, glassy carbon electrode as the working electrode (GCE, ID = 3 mm; model CHI104, CH Instruments Inc., USA) with area of 0.07cm<sup>2</sup> was used. The reference electrode was Hg/Hg<sub>2</sub>Cl<sub>2</sub> electrode soaked in saturated KCl(aq) and the counter electrode was platinum electrode(6.08 cm<sup>2</sup>). The method for cyclic voltammetric determination was conducted as described elsewhere [36,37]. To prevent taking place of water electrolysis, the scan voltage ranges and scan rate were set to be -1.5V ~ +1.5V and 10mV s<sup>-1</sup>, respectively. Prior to the testing without any interference, the glassy carbon electrode (GCE, ID = 3 mm; model CHI104, CH Instruments Inc.,

USA) was successively polished with 0.05 mm alumina polish and then rinsed with 0.5 M H<sub>2</sub>SO<sub>4</sub> and deionized water. Closed-loop areas of redox potential in CV curve were evaluated as indicators of electrochemical potentials using Origin 8. To quantitatively evaluate electrochemical capabilities of candidate biomaterial(s), areas of redox potential curves in closed CV loops (i.e., Area =  $\int_{V_L}^{V_H} (i_H - i_L) dV$ ) were

determined as an indicator for comparative assessment via SigmaPlot 10.0.

## 2.3. Double chamber-microbial fuel cells (DC-MFCs)

Regarding double chamber (DC)-MFC operation [38], the soaking areas of the graphite anode and cathode (grade, IGS743; Central Carbon Co., Ltd.) with culture broth or electrolyte solutions were ca. 0.001649 m<sup>2</sup> (i.e., the cathode and anode chamber of operating volume 200 mL) were selectively isolated by proton exchange membrane (DuPont Nafion® NR-212) in an immersed area of ca. 0.000452 m<sup>2</sup> (ID = 1.2 cm). LB broth medium (Difco LB Broth, Miller; Luria-Bertani) used for microbial growth in batch cultures and the MFC chamber is contained 10 g/L tryptone, 5 g/L yeast extract, and 10 g/L NaCl. LB medium consisted of essential nutrients of cell growth and energy consumption for the metabolism of electron-transport chain. The electroactive microorganism-*Shewanella haliotis* WLP72 (originally enriched and isolated to have the most favorable capabilities of color removal of azo dyes) was chosen. For double chamber MFCs, the cathodic chamber consisted of 6.38 g of K<sub>3</sub>Fe(CN)<sub>6</sub> (potassium ferricyanide; BAKER ANALYZED, A.C.S. Reagent) and 17.42 g of K<sub>2</sub>HPO<sub>4</sub> (dipotassium hydrogen phosphate; SHOWA Co. Ltd.) that were completely dissolved in 200 mL of distilled-deionized water. MFCs were performed at room temperature

(25°C). Inoculated bacterium WLP72 obtained from an isolated colony on an LB-streak agar plate was chosen for 12 h overnight (O/N) pre-culture in LB broth medium using a water bath shaker (Shinkwang, SKW-12; 30°C, 125 rpm). Next, 1% (v/v) sub-cultured broth was inoculated into fresh autoclaved LB broth for a 12 h culture (pH was not

adjusted for these O/N flask subcultures). Test sample(s) (e.g., herbal extract) were then added in 200 mL of cell broth (OD<sub>600</sub> ~ 2.0-2.2) of the anodic chamber in double chamber MFC for quantitative evaluation of bioelectricity-generating performance.

For power-generating determination, time courses of electric current

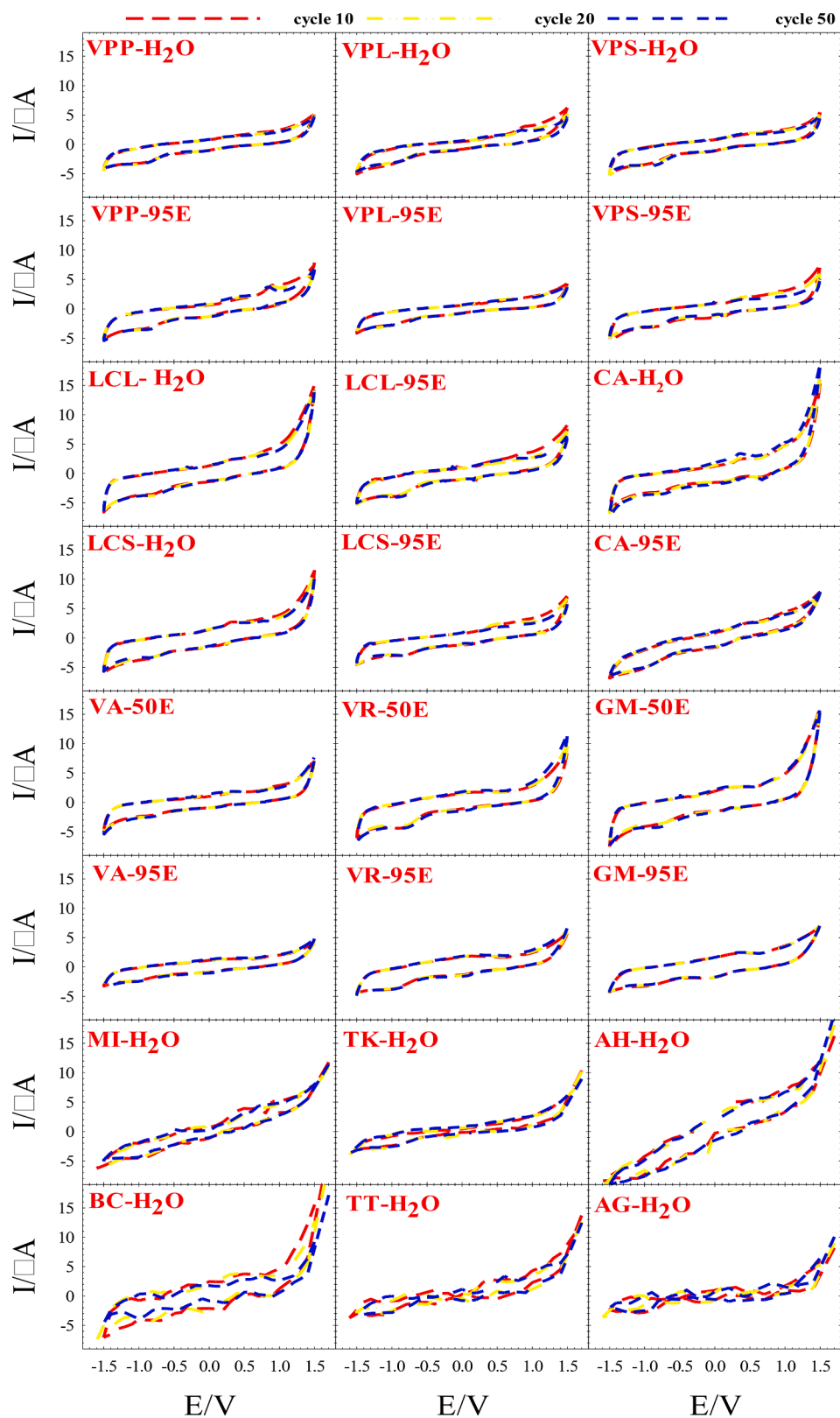


Fig. 1. Cyclic voltammetric profiles of different agricultural herb extracts of at cycle 10, 20 and 50.



( $I_{MFC}$ ) and voltage ( $V_{MFC}$ ) were automatically determined with a D/A system (DAS 5020; Jiehan Tech. Corp., Taiwan) [8,9]. To have identical basis for comparison, 1 K $\Omega$  external resistance was applied to MFCs. Power and current densities were determined by the formulae:

$$P_{\text{density}} = \frac{V_{MFC} \times I_{MFC}}{A_{\text{Anode}}}, \quad (1)$$

$$I_{\text{density}} = \frac{I_{MFC}}{A_{\text{Anode}}}, \quad (2)$$

where  $V_{MFC}$  and  $I_{MFC}$  could be evaluated with linear sweep voltammetry through a workstation for electrochemical analysis (Jiehan 5600, Jiehan Technology Corp., Taiwan). The parameter  $A_{\text{anode}}$  was the apparent working area of the graphite anode.

### 3. Results and discussion

#### 3.1. Cyclic voltammetry (CV)

As electroactive characteristics are significant to expression of ET-driven disease medication, serial cycles of CV simulated electro-oxidation and electro-reduction were thus taken place on samples for electrochemical reversibility and stability. That is, cyclic voltammogram trace upon reversible ET capabilities of agricultural herb extracts would quantitatively indicate whether their electrochemical activities were feasible to be electron shuttles (ESs) or antioxidants as electrochemical catalysts or electron donors, respectively. Aware that areas of “closed-loop” redox potential CV profiles could be quantitatively considered as their electrochemical activities. Stably reversible profiles of ESs or gradually attenuated sketches of antioxidants from distinct herbal extracts could suggest whether such herbal extracts were sustainable or unendurable for bioenergy/biorefinery applications, respectively. As prior studies [39,40] revealed, comparison upon more than 20 species of refreshing medicinal herbs indicated that electroactive medicinal herbs-*Syzygium aromaticum* (Ding xiang), *Citrus reticulata* (Chenpi) and *Lonicera japonica* (Jinyin hua) and *Camellia* green tea (*Camellia sinensis* (L.) Kuntze) were the most electroactive medicinal herbs due to the greatest area and most significant redox potential peaks displayed in CV profiles. As recent novel findings disclosed [11], chemicals bearing *ortho* or *para* dihydroxyl substituents on benzene ring and the flavonoid structure(s) would be the most favorable to mediate electron-shuttling features for bioenergy stimulation and antiviral “catalysis”. As abundant polyphenolics contents exist in herbal extracts, apparently herbal extracts tested herein would very likely contain such ES-behaved chemical compositions (e.g., chlorogenic acid, luteolin, rosmarinic acid, caffeic acid, protocatechuic acid, gallic acid) triggering their bioenergy-escalating as well as virus-resisting capabilities. To investigate whether test herbal extracts could be used as sustainable ESs for power augmentation in MFCs, feasibility study of long-term stability and reliability of CV assessment was thus implemented. As indicated in cyclic voltammogram profiles (Fig. 1), electrochemical activities of herbal extracts were gradually attenuated during 50 cycles of serial CV scans. In fact, after approx. 50 cycles of CV scan, such attenuated phenomena seemed to converge to asymptotically stabilized levels (data not shown). That is, after approx. 50 scan cycles, irreversible electron donors and/or acceptors (if present) in herbal extracts were inevitably oxidized or/and

reduced and only electrochemically stable, reversible and catalytic mediators and derived ES products were steadily persisted for long-term reuses. As Fig. 1 and Table 2 exhibited, after 50 cycles of CV scan gradually converged responses of electric current directly exhibited the stable endurance of electroactive ES species for ET-directed stimulation of bioelectricity generation in MFCs afterwards.

As a matter of fact, as Tsai et al., 2022 recently disclosed, anti-COVID-19 and/or antiviral capabilities of tradition Chinese medicine (TCM) were strongly associated with ET-related catalysis in herbal extracts [11]. For instance, brain-disorder medicines (e.g., L-DOPA, dopamine for PD treatment, epinephrine-associated and *ortho*-dihydroxyl ES(s)-based neurotransmitters for Huntington’s disease (HD)) were also possibly dealing with ET-mediated capabilities for disease treatment. These compounds are classified as ES compounds, which are reversible “catalysts” mediated between oxidized and reduced forms in electrochemical perspective. In fact, ES species would be more electrochemically available in anaerobic conditions, as oxygen is a very strong electron acceptor to competitively repress its electron-mediating characteristics. If polyphenolic antioxidants in TCM herbs could be effectively converted to be ES catalyst(s) in a higher degree, such persistent efficacy of herbal medication could consequently be maximized to guarantee efficacious disease treatment for human health. That is, synergistic conversion of ES species from antioxidant compounds present in anti-COVID-19 TCM would be significant to anti-viral characteristics to be expressed as Tsai et al. [11] revealed. These above-mentioned reasoning straightforwardly explains why comparative assessment upon agricultural herbs for bioelectricity-generating performance in MFCs will be of great importance to determine whether further screening upon such herbs with potential anti-viral or even anti-COVID-19 characteristics was reasonably recommended.

Aware that the scan rate of CV directly determined the reaction rate of serial electrochemical oxidation and reduction to be taken place in sampled herbal extracts. That is, different degrees of electro-degrading characteristics of chemical species present in herbal extracts would result in diverse responses of electrochemical activities (e.g., different conversion of electrochemical redox reactions) as indicated in Table 2 and Fig. 2. That is why larger areas of closed-loop CV diagrams in serial electrochemical analyses simply suggested more abundant easily degradable chemical species present to be electrochemically oxidized or reduced. As bioenergy-stimulating catalysts, ESs could usually display more symmetric oxidative and reductive potential peaks in reverse wave modes in CV profiles (i.e.,  $i_{pa}/i_{pc} \sim 1$ ). In fact, such definite quasi-reversible redox processes were specific fingerprint to respond different species and amounts of electroactive compositions in corresponding herbal extracts. That is, further MFC exploration in depth would still be inevitably required to quantitatively elucidate the efficiency of bioenergy expression. This bioenergy evaluation also distinguished the ES species from anti-oxidant/anti-reductant species and only herbal extracts with effective bioenergy-stimulating capabilities would be listed at top rank places. As indicated, top 5 ranking test herbal extracts were GM-50E (12.2 $\mu$ W), then CA-H<sub>2</sub>O (10.9 $\mu$ W), VPL-H<sub>2</sub>O (10.8 $\mu$ W), BC-H<sub>2</sub>O (10.4 $\mu$ W) and LCL-H<sub>2</sub>O (9.78 $\mu$ W). The last rank extract was VPP-H<sub>2</sub>O (3.35 $\mu$ W) only relatively higher than blank control-deionized water (1.2 $\mu$ W). These pointed out that top ranking extracts might contain more abundant electroactive species to be irreversibly oxidized or reduced or reversibly electron-shuttling. Last rank

**Table 2**

Comparison of closed-loop areas of CV profiles at cycle 10, 20, 50 using different agricultural waste extracts.

Area ( $\mu$ W)	VPP-H <sub>2</sub> O	VPP-95E	LCL-H <sub>2</sub> O	LCL-95E	VA-50E	VA-95E	MI -H <sub>2</sub> O	BC -H <sub>2</sub> O
Cycle 10/20/50	3.75/3.33/3.35	5.44/4.82/5.16	10.0/9.80/9.78	4.84/5.03/5.05	6.34/6.58/6.87	5.10/5.24/5.69	5.47/4.76/4.88	10.4/9.41/5.94
Area ( $\mu$ W)	VPL-H <sub>2</sub> O	VPL-95E	LCS -H <sub>2</sub> O	LCS-95E	VR-50E	VR -95E	TK -H <sub>2</sub> O	TT -H <sub>2</sub> O
Cycle 10/20/50	8.88/8.87/10.8	5.84/5.67/5.71	9.31/8.92/8.53	6.80/6.85/7.17	8.50/8.47/9.73	7.37/7.54/8.18	2.88/3.80/4.44	4.73/4.69/3.99
Area ( $\mu$ W)	VPS -H <sub>2</sub> O	VPS-95E	CA-H <sub>2</sub> O	CA-95E	GM -50E	GM -95E	AH -H <sub>2</sub> O	AG -H <sub>2</sub> O
50 Cycle 10/20/50	9.31/9.33/9.78	6.23/6.42/6.34	9.13/9.54/10.9	7.00/6.91/7.16	11.5/11.3/12.2	8.31/8.13/8.09	6.15/9.42/8.71	3.56/3.74/3.40

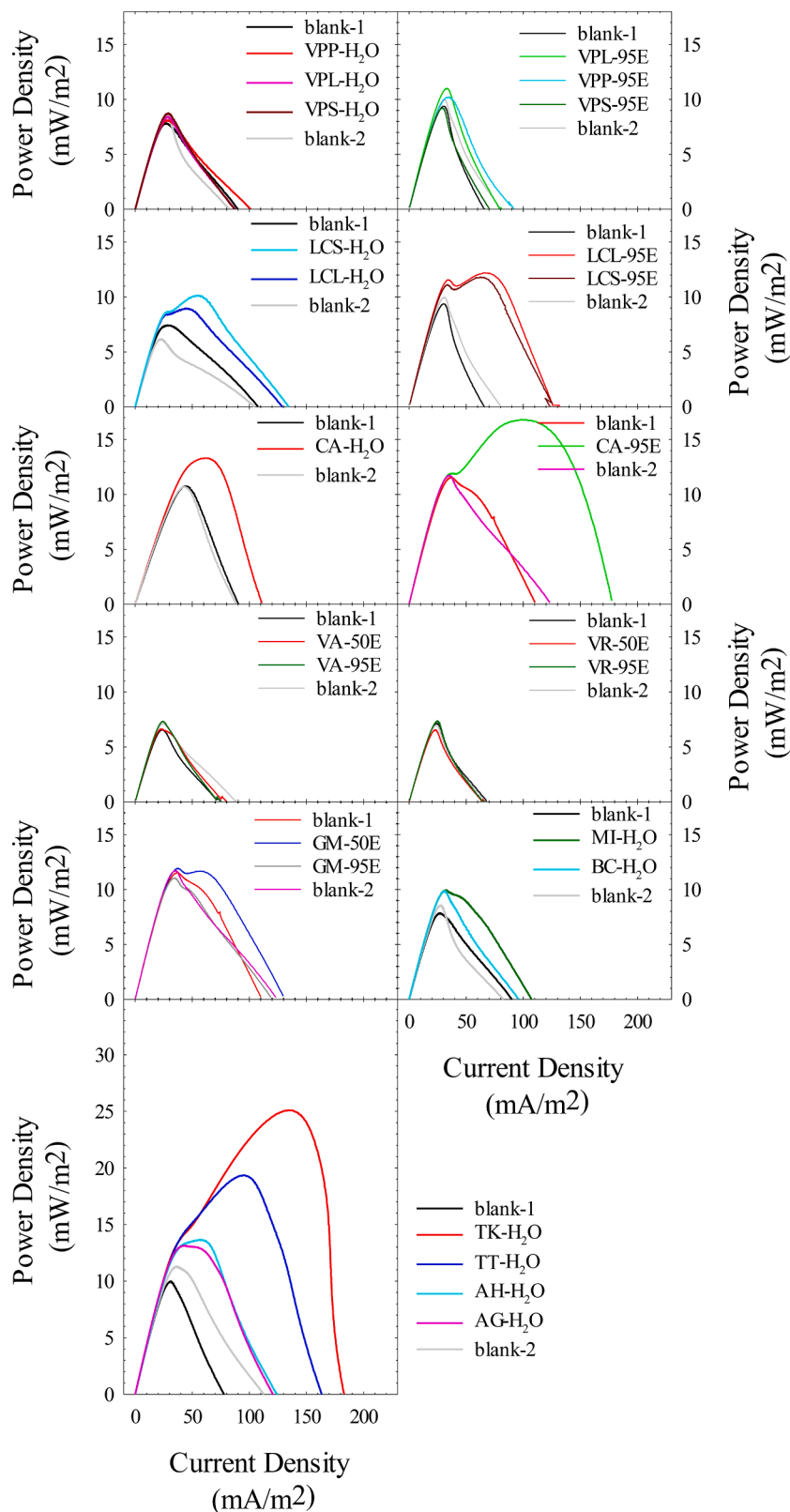
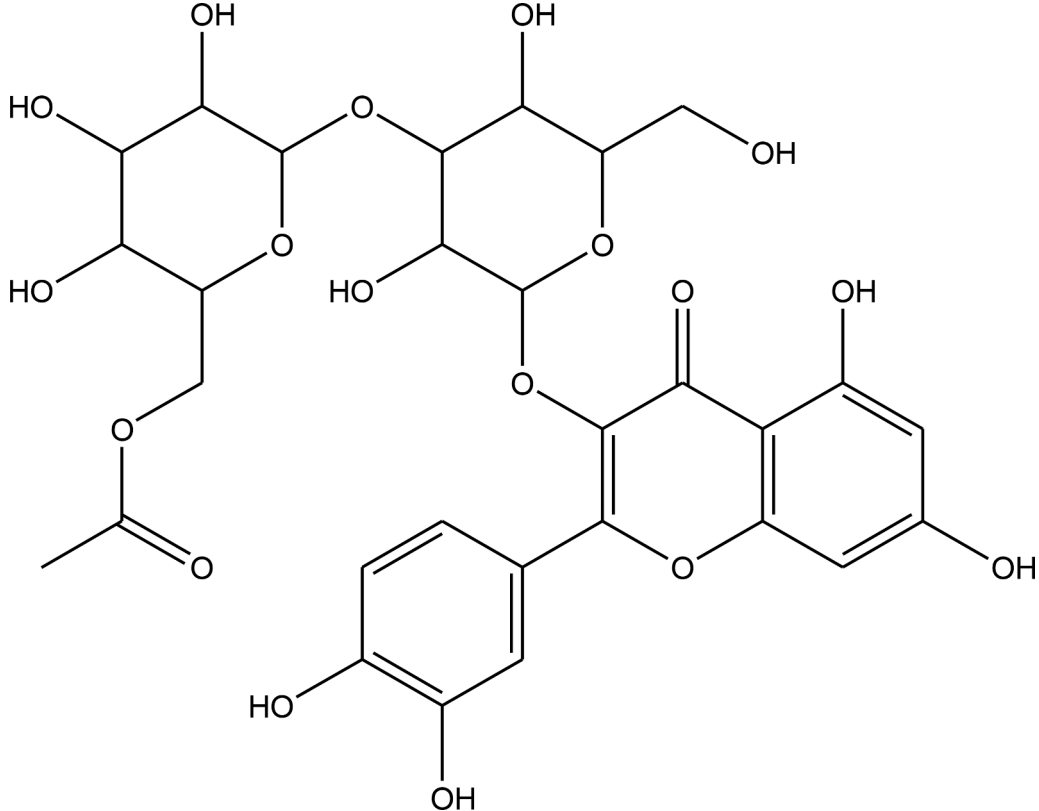


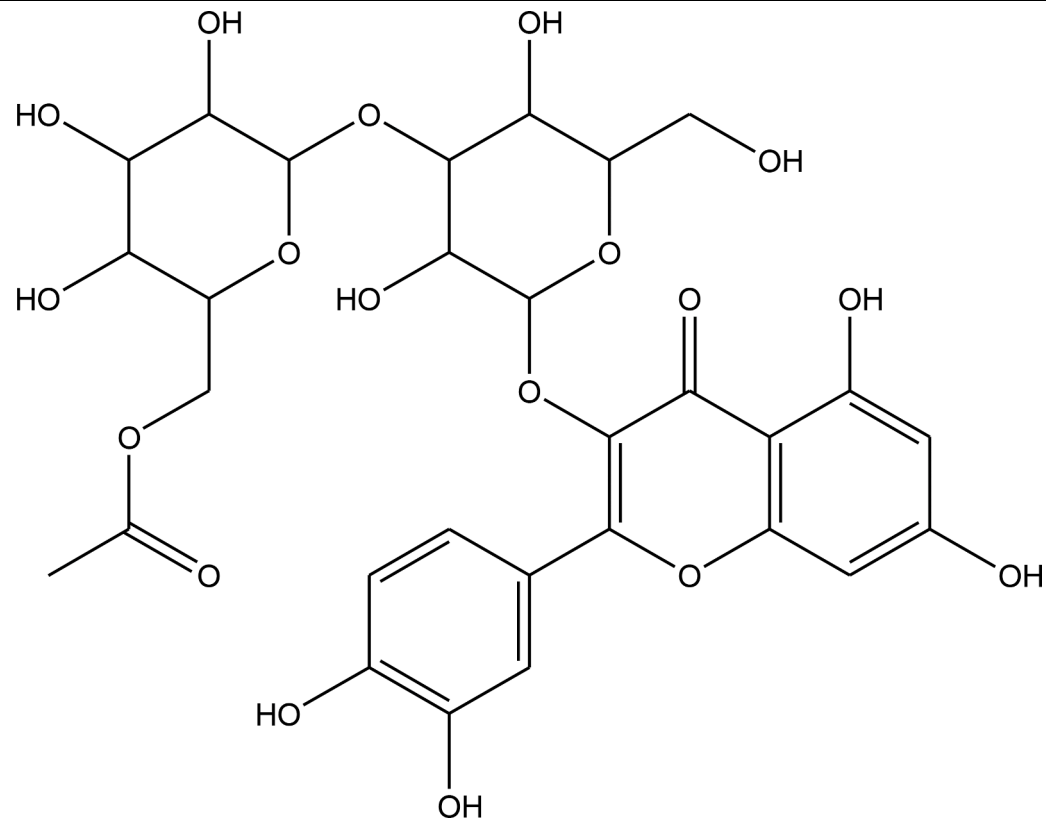
Fig. 2. Comparative profiles of power generation of agricultural waste extracts using MFC as a platform of bioenergy evaluation.

extract(s) suggested that the least abundance of electroactive species existed in such extract samples possibly due to a lack of bioenergy content species. However, all electrochemical extent in the herbal extract does not entail to be entirely biomass energy convertible. To correctly identify whether such electrochemical activities would be

effectively expressed by electrochemically appropriate microbes for practicability of bioenergy contents. Microbial fuel cells (MFCs) as the evaluation platform of biomass energy were implemented to definitely disclose if such electroactive potentials could be biologically converted or mediated to be ET-based catalysis as indicated afterwards in [Section](#)

**Table 3**  
Active constituents of *T. khasianum* and *E. hirta* with electron shuttles property for anti-COVID-19.

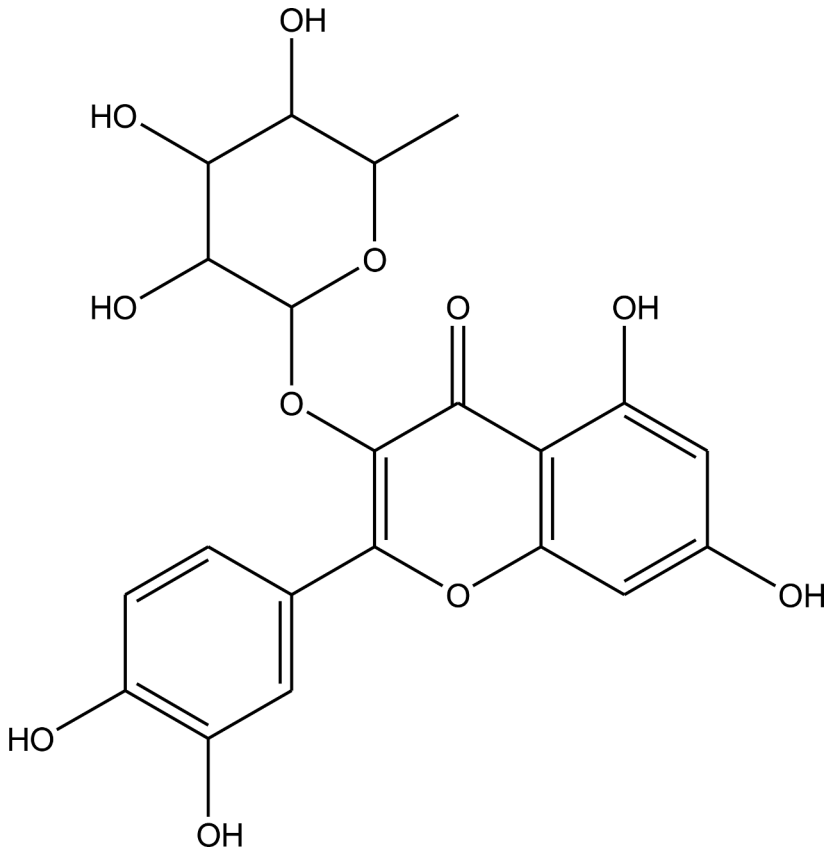
Plant	Compound	Chemical Structure	Refs.
<i>E. hirta</i>	Euphrobianin		[40,42]

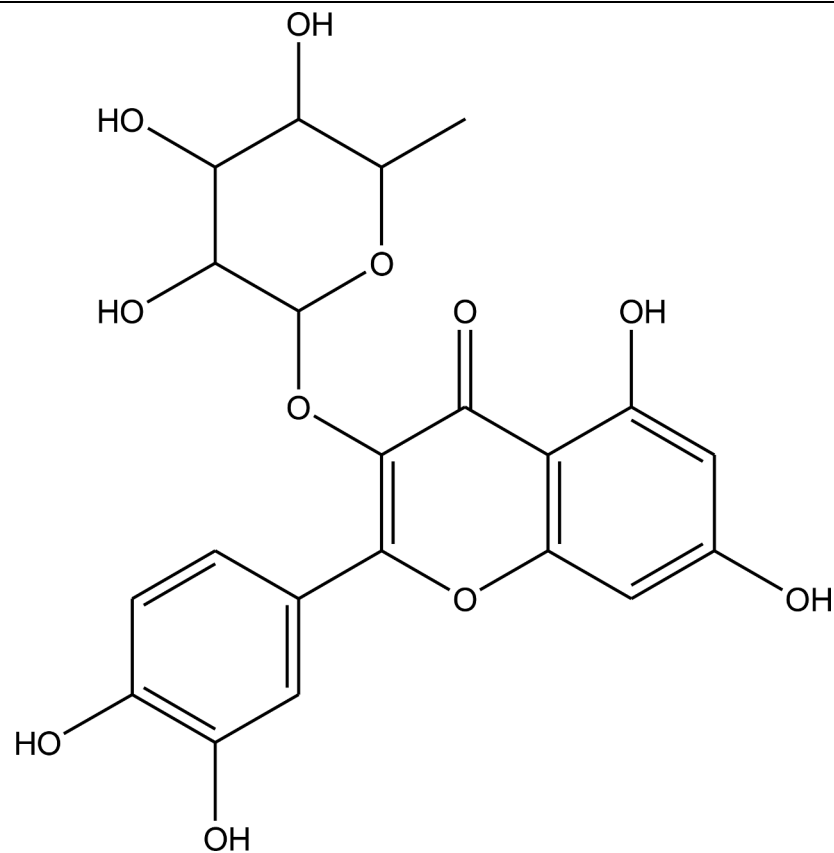


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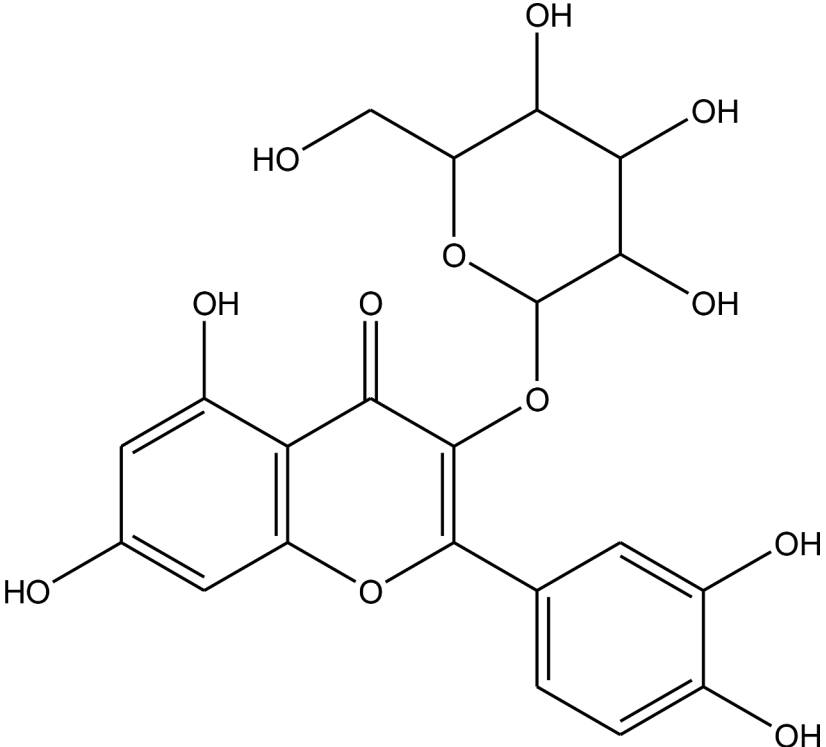
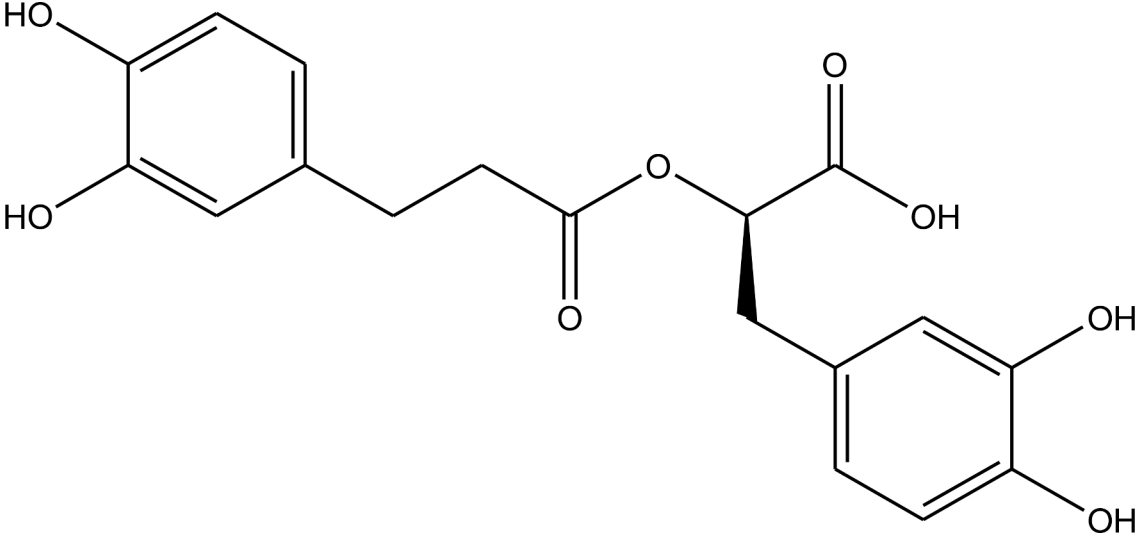
Table 3 (continued)

Plant	Compound	Chemical Structure	Refs.
	Quercetin 3-O-alpha-rhamnoside		



(continued on next page)

Table 3 (continued)

Plant	Compound	Chemical Structure	Refs.
	Isoquercitrin	 <p>The structure shows a central flavan-3-ol core (quercetin) with a glucose molecule attached to the C-3 position via an ether linkage. The glucose is in its cyclic pyranose form, with hydroxyl groups at C-2, C-3, C-4, and C-6, and a hydroxymethyl group at C-5.</p>	
<i>T. khasianum</i>	Rosmarinic acid	 <p>The structure shows a central biphenyl core with two hydroxyl groups on each phenyl ring. A propyl chain connects the two rings, and a butyric acid chain is attached to the propyl chain. The butyric acid chain is shown with a wedge bond to the chiral center, indicating its stereochemistry.</p>	[52]

3.2. Note that such ET-oriented bioenergy expression was very likely the milestone indicator to determine the efficacy of disease treatment (e.g., anti-viral activities) (Table 3).

### 3.2. Double chamber microbial fuel cells (DC-MFCs)

As prior study [11] indicated, electrochemically-promising biocatalysts (i.e., ESs) could not be consumed in cellular metabolism and remain intact before and after biochemical treatment. When ES-behaved drugs (e.g., *o*-dihydroxyl substituents (*o*-diOH) bearing levodopa for PD treatment and dopamine for HD treatment) were of great significance to clinical medication, such drugs of course own long-term capabilities to persist drug efficacy for disease treatment. Moreover, *o*-diOH and flavonoid-bearing chemical species (e.g., quercetin, rutin, fisetin, luteolin) in herbal extracts were found to be not only efficacious antiviral drug, but also effective ES species for clinical treatment. As an electrochemical catalyst apparently ES provides an alternative reaction route with lower activation energy than that of the non-catalyzed pathway. Therefore, ES drugs can speed up redox reactions by delivering more electrochemically favorable pharmacokinetics than those that exist in their absence to guarantee a promising efficacy of disease treatment. That is, in electrochemical terms, ES drugs also play vital roles in increasing ET efficiency between electron donors and acceptors for not only sustainable bioenergy extraction, but also enduring drug medication. That is why using MFCs, bioelectricity-generating capabilities evaluated via MFCs could be considered as prerequisite to prescreen the most appropriate herbal extract(s) for further feasibility to treat various infectious diseases (e.g., COVID-19).

Regarding MFC bioenergy assessment, the rankings of bioelectricity-generating capabilities (i.e., power density (PD) in the unit of  $\text{mW m}^{-2}$ ) of these herbal extracts were shown as follows (subscript was amplification factor with respect to the blank):

- (1) **MFC-A:MI-H<sub>2</sub>O** ( $9.95 \pm 0.21_{1.27 \pm 0.05}$ ) > BC-H<sub>2</sub>O ( $9.89 \pm 0.22_{1.23 \pm 0.05}$ ) > VPS-H<sub>2</sub>O ( $8.76 \pm 0.23_{1.12 \pm 0.05}$ ) > VPL-H<sub>2</sub>O ( $8.43 \pm 0.20_{1.07 \pm 0.05}$ ) > VPP-H<sub>2</sub>O ( $8.13 \pm 0.18_{1.04 \pm 0.04}$ ) > blank ( $7.85 \pm 0.16_{1.00}$ );
- (2) **MFC-B:TK-H<sub>2</sub>O** ( $25.09 \pm 0.83_{2.51 \pm 0.16}$ ) > TT-H<sub>2</sub>O ( $19.37 \pm 1.40_{1.94 \pm 0.20}$ ) > AH-H<sub>2</sub>O ( $13.69 \pm 0.70_{1.37 \pm 0.11}$ ) > AG-H<sub>2</sub>O ( $13.14 \pm 0.62_{1.32 \pm 0.10}$ ) > blank ( $9.98 \pm 0.29_{1.00}$ );
- (3) **MFC-C:LCS-H<sub>2</sub>O** ( $10.16 \pm 0.59_{1.36 \pm 0.14}$ ) > CA-H<sub>2</sub>O ( $10.13 \pm 0.52_{1.36 \pm 0.13}$ ) > LCL-H<sub>2</sub>O ( $8.87 \pm 0.47_{1.20 \pm 0.12}$ ) > blank ( $7.45 \pm 0.33_{1.00}$ );
- (4) **MFC-E:VA-95E** ( $7.34 \pm 0.25_{1.12 \pm 0.08}$ ) > VA-50E ( $6.61 \pm 0.26_{1.10 \pm 0.08}$ ) > blank ( $6.58 \pm 0.24_{1.00}$ );
- (5) **MFC-F:VR-95E** ( $7.38 \pm 0.14_{1.05 \pm 0.04}$ ) > blank ( $7.00 \pm 0.15_{1.00}$ ) > VR-50E ( $6.60 \pm 0.21_{0.94 \pm 0.05}$ );
- (6) **MFC-G:LCL-95E** ( $12.22 \pm 0.93_{1.30 \pm 0.13}$ ) > LCS-95E ( $11.83 \pm 0.87_{1.26 \pm 0.12}$ ) > VPL-95E ( $11.02 \pm 2.36_{1.17 \pm 0.28}$ ) > VPS-95E ( $10.73 \pm 2.30_{1.14 \pm 0.27}$ ) > VPP-95E ( $10.26 \pm 0.19_{1.09 \pm 0.05}$ ) > blank ( $9.39 \pm 0.23_{1.00}$ );
- (7) **MFC-H:CA-95E** ( $16.84 \pm 3.59_{1.46 \pm 0.54}$ ) > GM-50E ( $11.98 \pm 1.99_{1.04 \pm 0.34}$ ) > blank ( $11.57 \pm 1.83_{1.00}$ ) > GM-95E ( $11.12 \pm 2.06_{0.96 \pm 0.33}$ ).

As above-mentioned PD ranking and CV data in Section 3.1 indicated, although extracts of *Glycine max* (GM-50E) in different portions owned high electrochemical activities, biomass power-generating efficiencies were considerably not expressed with respect to blank level (ca. 0.96-1.04 fold) likely due to high biotoxicity potency and/or inconsistency to biological activities. In contrast, *Coffea arabica* (CA-H<sub>2</sub>O) water extract could reach 1.36 fold amplification factor of PD. Both the electrochemical activity and PD amplification in higher values straightforwardly implied that most of electrochemically active compositions in the extract were dominant in ET-oriented ES species with relatively low biotoxicity. That is, MFC analysis could exhibit not only biomass energy-

stimulating, but also cell metabolism-functioning performance. For instance, regarding aerobic bacteria effective biomass energy expression at least unveiled the non-resisting completion of cellular metabolism of glycolysis (i.e., glucose → pyruvate + NADH), citric acid cycle (i.e., pyruvate → CO<sub>2</sub>+NADH) and electron transport chain (i.e., NADH + O<sub>2</sub>→NAD+ water+ electrons+ proton gradient). The most electrochemically promising herbal extracts were *Trichodesma khasianum* (Jiǎ Suǎn Jiāng yè) (TK-H<sub>2</sub>O;  $2.51 \pm 0.16$  fold) and *Euphorbia hirta* (Fēi Yáng Cǎo) (TT-H<sub>2</sub>O;  $1.94 \pm 0.20$  fold). According to twofold index of power amplification, these two herbs seemed to be the most appropriate candidate extract sources of anti-COVID-19 drugs. As literature indicated, the conclusive remarks could be confirmed the following reasoning: (a) major content of *T. khasianum* was rosmarinic acid (i.e., *o*-diOH bearing ES) and (b) predominant compositions of *E. hirta* were euphrobinin, quercetin, quercetin 3-O-alpha-rhamnoside, isoquercitrin, and rutin (i.e., *o*-diOH bearing ESs). Due to abundance in biocompatible ES species, these two herbal extracts could be considered to be top-priority selection for anti-COVID-19 drugs [30,41,42].

### 3.3. Significance of study

Regarding the agricultural waste samples intentionally selected for this study, *Artocarpus heterophyllus* (pāramitā) seeds extract showed the antioxidant activity using DPPH, reducing power assay, lipid peroxidase, superoxide radical scavenging, and nitric oxide scavenging assays [21]. *Asystasia gangetica* (Chinese Violet) aerial parts, the extract of *A. gangetica* using extraction of different solvents contain biologically chemical components that contribute to its pharmacological activities, such as antioxidant and anti-inflammatory activities [22,43]. *Bombax ceiba* flowers (mù mián huā) extract have been examined through phytochemical screening tests to exhibit with antioxidant and antidiabetic activities [44]. The major compounds of *Coffea arabica* leaves have been identified using LC-MS which present as catechin or epicatechin, mangiferin or isomangiferin, procyanidin B, caffeoylquinic acids (CQA), caffeine, quercetin-3-O-glucoside, procyanidin C, rutin, and 3,4-diCQA. In addition, these chemical compositions of *C. arabica* leaves extracts could present strong antioxidant activity and other biological activities [45]. Some types of beans- *Glycine max* seeds, *Vigna angularis* seeds and *Vigna radiata* seeds contained phytochemical contents of polyphenols, flavonoids, condensed tannins and polysaccharides. Furthermore, 95% ethanol extract of *V. angularis* also showed biological activities such as antioxidant, anti-inflammatory, and cell viability [46]. *Litchi chinensis* leaves and *Litchi chinensis* stems own considerable antioxidant activity of the aqueous and organic extracts of leaves and stem which was investigated using 2,2'-azinobis(3-ethylbenzothiazoline6-sulphonic acid) (ABTS) decolorization assay, the ferric reducing anti-oxidant power (FRAP) assay and 2,2'-diphenyl-1-picrylhydrazil (DPPH) assay [28]. Chemical compositions of *Mangifera indica* peels are phenolic compounds such as gallic acid, pyrogallol, chlorogenic acid, *p*-hydroxybenzoic acid, *p*-coumaric acid, ECG, and CG. Undeniably, these compounds showed antioxidant, anti-inflammatory and antibacterial activities [29]. *Vanilla planifolia*, the pods of *V. planifolia* are used as vanilla flavoring in food. In fact, the ethanol extracts of *V. planifolia* pods have been showed with antioxidant activity [47]. Moreover, considering *V. planifolia* leaves, the antiproliferative property of *V. planifolia* leaves inhibited A431 skin cancer cell line by MTT assay [48]. *Trichodesma khasianum* is an endemic plant in Taiwan. The traditional use of *T. khasianum* is to treat ulcers and hypertension in folkloric medicine for aboriginal Puyuma (Pi Lâm-tsók) people in Taiwan. Pretreatment of *T. khasianum* 80% ethanol extract with dosage at mg/kg b.w. basis showed that inflammatory and antioxidant activity [30,49]. *Euphorbia hirta* aerial parts (Fēi Yáng Cǎo), the dried aerial parts extracts of *E. hirta* showed the antioxidant property using DPPH and FRAP assays, and its anti-diabetic activity were evaluated by glucose uptake assay [50]. *E. hirta* widely distributed in Asia, it has been found for many biological activities which including antioxidant, anti-bacterial, anti-venom,

antimalarial and antiviral (e.g., HIV, DANV, HSV activities) [41,42,51]. The literatures have been reported for *E. hirta* anti-COVID-19 activity using two different targets of SARS-CoV-2, namely Main protease (Mpro; PDB ID: 6M2N) and RNA-dependent RNA polymerase (RdRp; PDB ID: 7BW4) recently. The results indicated that the major constituents of *E. hirta* are euphorbianin, quercetin 3-o-alpha-rhamnoside, isoquercitrin, and rutin. These flavonoid compound euphorbianin and rutin has higher binding affinity against targets than others. Although *T. khasianum* still has no scientific reports for any antiviral study, but the major constituent rosmarinic acid has been showed high binding affinity with control 2-DG and nafamostat against ACE2 and TMPRSS2 [52]. In our previously studies indicated that *Camellia* green tea extract has more stimulate bioenergy utilization (e.g., 176% increase in maximum power density) using MFC, especially unfermented *Camellia* tea extract (i.e. green tea) has the ESs for increasing bioenergy extraction compared to other herbs [6,53]. The major constituent EGCG of green tea showed that anti-COVID-19 activity which could activate Nrf2 pathway and suppress ACE2 and TMPRSS2 [54]. It was thus suggested that PD would be correlated with antiviral activity. It was speculated that *E. hirta* and *T. khasianum* could have the potential anti-COVID-19 activity with electron-shuttling characteristics.

Moreover, the inconsistent ranking of herbal power densities and corresponding CV areas at least was due to the following reasons: (a) Biotoxicity: herbal extracts might have biotoxicity potency to electroactive bacteria, influencing bioelectricity-generating characteristics in MFCs; (b) Electrochemical potential: diverse distributions of electroactive chemical species and contents in herbal extracts would result in distinct levels of ES-like chemical(s) present for power-generating expression; (c) Abiotic versus biological expression: abiotic CV offered synthetic electron-donating and withdrawing processes for redox reactions to be taken place; however, whether such processes could be biocompatible to receptor microbes for bioenergy augmentation still limits in the nature of chemical species acceptable to microbial tolerance or resistance; (d) Discrepancy of electrochemical potentials: although CV profiles of herbal extracts seemed to be relatively electrochemically stable, unbalanced antioxidant/anti-reductant activities might not be completely converted for ET catalysis and MFC capability.

Regarding electrochemically favorable PK (refer to "US EPA Toxicology Handbook"), pharmacokinetics (PK) studied the fate of drugs administered to receptor organisms, the process of the uptake of drugs by the body, the biotransformation of drugs and derived metabolites to be undergone and delivered, distributed and eliminated. When electrochemically active ES catalysts were provided, such redox-mediating catalysts could change the rate of chemical reaction(s) through an alternative reaction pathway with lower activation energy than non-catalysis-oriented mechanism. That is, ES drugs could mediate shuttling electrons to speed up redox reactions by delivering more electrochemically active electrons to guarantee a more promising efficacy of disease treatment. Due to electrochemical catalysis of ES drugs, disease treatment could be stably persisted, leading to its promising clinical effectiveness and efficacy. However, the benefit of a drug should take into account both the beneficial response (efficacy) and adverse effect (safety). As literature exhibited, compound medicine with favorable pharmacokinetics is more likely to be efficacious and safe (e.g., Singh SS "Preclinical Pharmacokinetics: An Approach Towards Safer and Efficacious Drugs" Current Drug Metabolism, 2006, 7, 165-182). Further PK should consider more performance indices to emphasize appropriate dose-response curves for practicability of clinical trials. For example, the closeness of the beneficial and the adverse dose-response curves is described by therapeutic index (TI), which is the ratio of the mid-points of two curves:  $TI = TD_{50}/ED_{50}$ , where  $TD_{50}$  denoted toxic dose to produce 50% of the maximum change of toxic effect in the exposed population and  $ED_{50}$  was the dose which produce 50% of an effect. When TI has a value of 10 or above, these two curves are well separated and doses for beneficial purposes are reasonably safe. This study also adopted MFC and CV evaluation platform of bioenergy and electrochemical content.

When both electrochemical indices showed high performances, it simply exhibited that abiotic electrochemical potentials could be highly biocompatible to be almost fully expressed in bioenergy-stimulating characteristics in MFCs. That is, this MFC/CV assessment provided a novel perspective to emphasize the significance of more electrochemically favorable PK in drug treatment.

In addition, the sustainable use of herbal medicine plays an important role for improving environmental friendliness today. All of cradle-to-cradle bioresource recycling and reuses are of great significance for promoting green and sustainable development of herbal medicine industry. This study has been clearly indicated that *E. hirta* and *T. khasianum* could have the potential anti-COVID-19 activity with electron-shuttling characteristics for their other applications (e.g., supplements and drug development). *E. hirta* is perennial herb which widely distribute to Asia (e.g., Myanmar, Thailand, Indonesia, Malaysia, Papua New Guinea, Philippines and Taiwan). It is also part of the weed of cultivated fields, perennial crops, grasslands, roadsides, fallow lands, ditch banks and waste places [52]. *E. hirta* water extract has been reported to treat dengue fever for most symptoms and recovery stages. The dosage forms of *E. hirta* could be applied to clinical treatment and safety for dengue patients [55]. *T. khasianum* is even an endemic plant in Taiwan and using indigenous herbal species in Taiwan for wide-ranged applications also satisfied sustainable goals since Taiwan's ecological integrity is remained intact. Traditional aboriginal cuisines are use the leaves of *T. khasianum* to wrap millets and meat (cinavu in Paiwan language). The leaves of *T. khasianum* could be administered to supplement the blood, treat ulcers, and be antihypertensive in aboriginal folkloric uses [49]. Limited scientific evidences have been showed that leaves of *T. khasianum* 80% EtOH extracts have the antioxidant, anti-inflammatory effects and protect gastric mucosal injury [30,49]. The material resources of *E. hirta* and *T. khasianum* have low cost to cultivate which could easy to collect and widely distribute in Taiwan. Here, the sustainable use of medicinal plant resources and the ways to achieve their sustainability was also exhibited. Drugs and therapeutics originally obtained from the plants are usually considered to be economically feasible and cost effective and it was believed that natural herbs were even less toxic than synthetic chemicals. This study indicated that *E. hirta* and *T. khasianum* apparently have the pharmacological value on their green sustainability.

#### 4. Conclusion

Cyclic voltammetric profiles of herbal extracts seemed to be not strongly correlated with bioenergy-generating performance using double chamber MFCs (DC-MFCs) possibly due to different potency of herbal toxicity. In addition, cyclic voltammogram only involved in abiotic electrochemical characteristics; however, DC-MFCs could directly respond biomass energy expression of receptor microbes. Based on two-fold index of power amplification, this study pointed out that *E. hirta* and *T. khasianum* were possible anti-COVID-19 herbal species selected from agricultural waste. With effective screening of new herbal drug development, this bioenergy-steered evaluation protocol (e.g., CV, MFC assessment) could help select herbal sources with medicinal potentials from agricultural waste and other natural sources.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## References

- Logan BE, Hamelers B, Rozendal R, Schröder U, Keller J, Freguia S, Aelterman P, Verstraete W, Rabaey K. Microbial fuel cells: methodology and technology. *Environ Sci Technol* 2006;40:5181–92. <https://doi.org/10.1021/es0605016>.
- Chen BY, Hsueh CC, Liu SQ, Hung JY, Qiao Y, Yueh PL, et al. Unveiling characteristics of dye-bearing microbial fuel cells for energy and materials recycling: redox mediators. *Int J Hydrogen Energy* 2013;38:15598–605. <https://doi.org/10.1016/j.ijhydene.2013.03.132>.
- Chen BY, Wu YC, Lin YH, Tayo LL, Tacas AC, Hsueh CC. Deciphering electron-shuttling characteristics of Parkinson's disease medicines via bioenergy extraction in microbial fuel cells. *Ind Eng Chem Res* 2020;59:17124–36. <https://doi.org/10.1021/acs.iecr.0c01062>.
- Huang ZL, Chen BY, Liu YC. Optimal stimulation of *Houttuynia cordata* herbal extract as electron shuttle for bioenergy extraction in microbial fuel cells. *J Taiwan Inst Chem Eng* 2020;114:47–56. <https://doi.org/10.1016/j.jtice.2020.09.026>.
- Xu B, Guo LL, Sun QJ, Qin LJ, Tsai PW, Hsueh CC, et al. Deciphering electrochemically promising electron-shuttling characteristics of hydrolysable tannin-abundant *Galla chinensis* for bioenergy generation in microbial fuel cells. *Biochem Eng J* 2019;151. <https://doi.org/10.1016/j.bej.2019.107318>. Article number 107318.
- Qin LJ, Guo LL, Xu B, Hsueh CC, Jiang M, Chen BY. Exploring community evolutionary characteristics of microbial populations with supplementation of *Camellia* green tea extracts in microbial fuel cells. *J Taiwan Inst Chem Engrs* 2020; 113:214–22. <https://doi.org/10.1016/j.jtice.2020.08.015>.
- Tacas ACJ, Tsai PW, Tayo LL, Hsueh CC, Sun SY, Chen BY. Degradation and biotoxicity of azo dyes using indigenous bacteria-acclimated microbial fuel cells (MFCs). *Process Biochem* 2021;102:59–71. <https://doi.org/10.1016/j.procbio.2020.12.003>.
- Chen BY, Hsueh CC, Liu SQ, Ng IS, Wang YM. Deciphering mediating characteristics of decolorized intermediates for reductive decolorization and bioelectricity generation. *Bioresour Technol* 2013;145:321–5. <https://doi.org/10.1016/j.biortech.2012.12.164>.
- Chen BY, Liao JH, Hsueh CC, Qu ZW, Hsu AW, Chang CT, Zhang SP. Deciphering biostimulation strategy of using medicinal herbs and tea extracts for bioelectricity generation in microbial fuel cells. *Energy* 2018;161:1042–54. <https://doi.org/10.1016/j.energy.2018.07.177>.
- Chen BY, Liao JH, Hsu AW, Tsai PW, Hsueh CC. Exploring optimal supplement strategy of medicinal herbs and tea extracts for bioelectricity generation in microbial fuel cells. *Bioresour Technol* 2018;256:95–101. <https://doi.org/10.1016/j.biortech.2018.01.152>.
- Tsai PW, Hsieh CY, Ting JU, Ciou YR, Lee CJ, Hsieh CL, Lien TK, Hsueh CC, Chen BY. Synergistic deciphering of bioenergy production and electron transport characteristics to screen traditional Chinese medicine (TCM) for COVID-19 drug development. *J Taiwan Inst Chem E* 2022;135:104365. <https://doi.org/10.1016/j.jtice.2022.104365>.
- Kirby AJ, Schmidt R. The antioxidant activity of Chinese herbs for eczema and placebo herbs. *J Ethnopharmacol* 1997;56(2):103–8. [https://doi.org/10.1016/S0378-8741\(97\)01510-9](https://doi.org/10.1016/S0378-8741(97)01510-9).
- Benavente-garcia O, Castillo J, Lorente J, Del Rio JA. Antioxidant activity of phenolics extracted from *Olea europaea* L. leaves Benavente. *Food Chem* 2000;68: 457–62. [https://doi.org/10.1016/S0308-8146\(99\)00221-6](https://doi.org/10.1016/S0308-8146(99)00221-6).
- Cao YH, Cao RH. Angiogenesis inhibited by drinking tea. *Nature* 1999;398(6726): 381–8.
- Capecka E, Mareczek A, Leja M. Antioxidant activity of fresh and dry herbs of some *Lamiaceae* species. *Food Chem* 2005;93:223–6. <https://doi.org/10.1016/j.foodchem.2004.09.020>.
- Kahkonen MP, Hopia AI, Vuorela HJ, Rauha JP, Pihlaja K, Kujula TS. Antioxidant activity of plant extracts containing phenolic compounds. *J Agric Food Chem* 1999; 47:3954–62. <https://doi.org/10.1021/jf990146l>.
- Solnier J, Fladerer JP. Flavonoids: a complementary approach to conventional therapy of COVID-19? *Phytochem Rev* 2021;20:773–95. <https://doi.org/10.1007/s11101-020-09720-6>.
- Li X, Xu ZX, Ming YL. Application of chinese herbal medicine in prevention and treatment of corona virus disease 2019. *Subtropical Plant Sci* 2020;49(2):83–92. <https://doi.org/10.3969/j.issn.1009-7791.2020.02.001> (In Chinese).
- Huang YF, Bai C, He F, Xie Y, Zhou H. Review on the potential action mechanisms of chinese medicines in treating coronavirus disease 2019 (COVID-19). *Pharmacol Res* 2020;158:104939. <https://doi.org/10.1016/j.phrs.2020.104939>.
- Ning F, Ou SJ, Lee YL. Cognitive research on the development of agricultural waste resource treatment technology for a sustainable environment. *IOP Conf Ser Earth Environ Sci* 2021;012002. <https://doi.org/10.1088/1755-1315/811/1/012002>. Article number.
- Sreeja Devi PS, Kumar NS, Sabu KK. Phytochemical profiling and antioxidant activities of different parts of *Artocarpus heterophyllus* Lam. (Moraceae): a review on current status of knowledge. *Future J Pharm Sci* 2021. <https://doi.org/10.1186/s43094-021-00178-7>. Article number 30.
- Barbaza MYU, De Castro-Cruz KA, Hsieh CL, Tsai PW. Determination of the chemical constituent contents and antioxidation properties of *Asystasia Gangetica*. *Indian J Pharm Educ Res* 2021;55:863–71. <https://doi.org/10.5530/ijper.55.3.160>.
- Chaudhary Pankaj Haribhau, Tawar Mukund Ganeshrao. Pharmacognostic and Phytopharmacological Overview on *Bombax ceiba*. *Sys Rev Pharm* 2019;10(1): 20–5. <https://doi.org/10.5530/srp.2019.1.4>.
- Ngamsuk S, Huang T-C, Hsu J-L. Determination of Phenolic Compounds, Procyanidins, and Antioxidant Activity in Processed *Coffea arabica* L. Leaves. *Foods* 2019;8(9). <https://doi.org/10.3390/foods8090389>. Article number 389.
- Mekam PN, Martini S, Nguetack J, Tagliacucchi D, Stefani E. Phenolic compounds profile of water and ethanol extracts of *Euphorbia hirta* L. leaves showing antioxidant and antifungal properties. *S Afr J Bot* 2019;127:319–32. <https://doi.org/10.1016/j.sajb.2019.11.001>.
- Peiretti PG, Karamač M, Janiak M, Longato E, Meineri G, Amarowicz R, Gai F. Phenolic composition and antioxidant activities of soybean (*Glycine max* (L.) Merr.) plant during growth cycle. *Agronomy* 2019;9(3). <https://doi.org/10.3390/agronomy9030153>. Article number 153.
- Mir H, Perveen N. Phyto-chemistry and therapeutic potential of litchi (*Litchi chinensis* Sonn.): an age-old ingredient in traditional medicine. *Indian J Tradit Knowl* 2022;21(1):29–39.
- Khan IU, Asghar MN, Iqbal S, Bokhari TH, Khan ZUD. Radical scavenging and antioxidant potential of aqueous and organic extracts of aerial parts of *Litchi chinensis* Sonn. *Asian J Chem* 2009;2(7):5073–84.
- Huang CY, Kuo CH, Wu CH, Kuan AW, Guo HR, Lin YH, Wang PK. Free radical-scavenging, anti-inflammatory, and antibacterial activities of water and ethanol extracts prepared from compressional-puffing pretreated mango (*Mangifera indica* L.) peels. *J Food Qual* 2018. <https://doi.org/10.1155/2018/1025387>. Article ID 1025387.
- Wang GY, Chen SY, Chen YY, Hong CJ, Hsu YH, Yen GC. Protective effect of rosmarinic acid-rich *Trichodesma khasianum* clarkle leaves against ethanol-induced gastric mucosal injury *in vitro* and *in vivo*. *Phytomedicine* 2021;80:153382.
- Luo J, Cai W, Wu T, Xu B. Phytochemical distribution in hull and cotyledon of adzuki bean (*Vigna angularis* L.) and mung bean (*Vigna radiata* L.), and their contribution to antioxidant, anti-inflammatory and anti-diabetic activities. *Food Chem* 2016;201:350–60. <https://doi.org/10.1016/j.foodchem.2016.01.101>.
- Guo F, Zhang S, Yan X, Dan Y, Wang J, Zhao Y, Yu Z. Bioassay-guided isolation of antioxidant and  $\alpha$ -glucosidase inhibitory constituents from stem of *Vigna angularis*. *Bioorg Chem* 2019;87:312–20. <https://doi.org/10.1016/j.bioorg.2019.03.041>.
- Palama TL, Fock I, Choi YH, Verpoorte R, Kodja H. Biological variation of *Vanilla planifolia* leaf metabolome. *Phytochemistry* 2010;71(5-6):567–73. <https://doi.org/10.1016/j.phytochem.2009.12.011>.
- Menon S, Nayeem N. *Vanilla Planifolia*: a review of a plant commonly used as flavouring agent. *Int J Pharm Sci Rev Res* 2013;20(2):225–8.
- Velankar MH, Heble MR. Biotransformation of externally added vanillin related compounds by multiple shoot cultures of *Vanilla planifolia* L. *J Plant Biochem Biotechnol* 2004;13:153–6. <https://doi.org/10.1007/BF03263213>.
- Guo LL, Qin LJ, Xu B, Wang XZ, Hsueh CC, Chen BY. Deciphering electron-shuttling characteristics of epinephrine and dopamine for bioenergy extraction using microbial fuel cells. *Biochem Eng J* 2019;148:57–64. <https://doi.org/10.1016/j.bej.2019.04.018>.
- Xu B, Guo LL, Sun QJ, Qin LJ, Tsai PW, Hsueh CC, Chen BY. Deciphering electrochemically promising electron-shuttling characteristics of hydrolysable tannin-abundant *Galla chinensis* for bioenergy generation in microbial fuel cells. *Biochem Eng J* 2019;151:107318. <https://doi.org/10.1016/j.bej.2019.107318>.
- Chen BY, Hsueh CC, Lin YH, Tayo LL, Sun SY, Hong JM, Cai PS. Deciphering interactive synergy of electron-transfer characteristics for optimal microbial fuel cell-steered dye decolorization. *J Taiwan Inst Chem Engrs* 2021;129:80–90. <https://doi.org/10.1016/j.jtice.2021.10.006>.
- Qin LJ, Guo LL, Xu B, Hsueh CC, Jing M, Chen BY. Exploring community evolutionary characteristics of microbial populations with supplementation of *Camellia* green tea extracts in microbial fuel cells. *J Taiwan Inst Chem Engrs* 2020; 113:214–22. <https://doi.org/10.1016/j.jtice.2020.08.015>.
- Hsueh CC, Wu CC, Chen BY. Polyphenolic compounds as electron shuttles for sustainable energy utilization. *Biotechnol Biofuels* 2019;12:271. <https://doi.org/10.1186/s13068-019-1602-9>.
- Khurshed A, Jain V, Wani AR. *Euphorbia hirta* as a gold mine of high-value phytochemicals: a comprehensive review of its pharmacological activities and possible role against SARS-CoV-2. *BMRAT* 2022;9(2):4930–49. <https://doi.org/10.15419/bmratt.v9i2.728>.
- Parmar G, Shah A, Shah S, Seth AK. Identification of bioactive phytoconstituents from the plant *Euphorbia hirta* as potential inhibitor of SARS-CoV-2: an *in-silico* approach. *Biointerface Res Appl Chem* 2022;12(2):1385–96. <https://doi.org/10.33263/BRIAC122.13851396>.
- Barbaza MYU, Hsieh CY, De Castro-Cruz KA, Lee CJ, Hsieh CL, Tsai PW. The potential of *Asystasia gangetica* (Chinese violet) extracts as an anti-aging agent and as a whitening agent. *Plant Cell Biotechnol Mol Biol* 2020;21(39-40):49–54.
- Kriintong N, Katisart T. *In vitro* antioxidant and antidiabetic activities of leaf and flower extracts from *Bombax ceiba*. *Phcog Res* 2020;12:194–8. <https://doi.org/10.4103/pr.pr.116.19>.
- Ngamsuk S, Huang TC, Hsu JL. Determination of phenolic compounds, procyanidins, and antioxidant activity in processed *Coffea arabica* L. Leaves. *Foods* 2019;8(9). <https://doi.org/10.3390/foods8090389>. Article number 389.
- Hsieh CY, Tsai JR, Lee CJ, Ciou YU, Li JS, Tayo LL, Tsai PW. Biological properties and phytonutrient profile of beans: *Vigna angularis*, *Vigna radiata*, and *Glycine max*. *Biointerface Res Appl Chem* 2022;13(1). <https://doi.org/10.33263/BRIAC131.053>. Article number 53.
- Chen CL, Ciou YR, Fu PW, Wu SK, Ko SY, Alimboyoguen AB, Tayo LL, Tsai PW. Phytochemical Content Analysis and Antioxidant Activity of *Vanilla planifolia* PODS. *Plant Cell Biotechnol Mol Biol* 2021;22(63-64):30–8.



- [48] Vijayababu K, Punnagai K. *In-vitro* anti-proliferative effects of ethanolic extract of *Vanilla planifolia* leaf extract against a431 human epidermoid carcinoma cells. *Biomed Pharmacol J* 2019;12(3):1141–6. <https://doi.org/10.13005/bpj/1742>.
- [49] Chen SY, Wang GY, Lin JH, Ye GC. Antioxidant and anti-inflammatory activities and bioactive compounds of the leaves of *Trichodesma khasianum* clarke. *Ind Crops Prod* 2020;151. <https://doi.org/10.1016/j.indcrop.2020.112447>. Article number 112447.
- [50] Aquino LBB, Barbaza MYU, Ramos JLT, Lee MJ, Ko SY, Hsieh CL, De Castro-Cruz KA, Tsai PW. Aerial Parts of *Euphorbia hirta* L. in polar and non-polar solvents: phytochemical, antioxidant and glucose uptake studies for potential source of adjunct drug for diabetes. *Trop J Nat Prod Res* 2020;4(10):708–13. <https://doi.org/10.26538/tjnpr/v4i10.9>.
- [51] Magozwi DK, Dinala M, Mokwana N, Siwe-Noundou X, Krause RWM, Sonopo M, McGaw LJ, Augustyn WA, Tembu VJ. Flavonoids from the genus euphorbia: isolation, structure, pharmacological activities and structure–activity relationships. *Pharmaceuticals* 2021;14. <https://doi.org/10.3390/ph14050428>. Article number 428.
- [52] Jindal D, Rani V. In silico studies of phytoconstituents from *Piper longum* and *Ocimum sanctum* as ACE2 and TMRSS2 inhibitors: strategies to combat COVID-19. *Appl Biochem Biotechnol* 2022. <https://doi.org/10.1007/s12010-022-03827-6>.
- [53] Chen BY, Liao JH, Hsueh CC, Qu Z, Hsu AW, Chang CT, Zhang S. Deciphering biostimulation strategy of using medicinal herbs and tea extracts for bioelectricity generation in microbial fuel cells. *Energy* 2018;161. <https://doi.org/10.1016/j.energy.2018.07.177>. Article number 1042e1054.
- [54] Zhang Z, Zhang X, Bi K, He Y, Yan W, Yang CS, Zhang J. Potential protective mechanisms of green tea polyphenol EGCG against COVID-19. *Trends Food Sci Technol* 2021;114:11–24. <https://doi.org/10.1016/j.tifs.2021.05.023>.
- [55] de Guzman GQ, Dacanay AT, Andaya BA, GJ Alejandro. Ethnopharmacological studies on the uses of *Euphorbia hirta* in the treatment of dengue in selected indigenous communities in Pangasinan (Philippines). *J Intercult Ethnopharmacol* 2016;5(3):239–43. <https://doi.org/10.5455/jice.20160330124637>.