

## Phytochemicals from *Siraitia grosvenorii*: New Minor Compounds and Advances in Pharmacological Activities

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### Abstract

*Siraitia grosvenorii*, also known as Monk Fruit or Luo Han Guo (in Chinese), is a popular medicinal plant used in Traditional Chinese Medicine for over hundreds of years with an array of amazing medicinal and nutritional benefits. It is indigenous to southern China, particularly Guangxi Province, and northern Thailand. The edible sweet fruits contain many phytochemicals; mainly cucurbitane triterpenoid glycosides or mogrosides, flavonoids and other bioactive constituents. These phytochemicals are responsible for various reported pharmacological activities of the plant. The first to be isolated were mogrosides about 35 years ago, while presently, more compounds and their metabolites are being characterized. Mogrosides are natural sweeteners, which are about 300 times sweeter than sucrose. Therefore, this review intends to highlight the recently identified new phytochemicals from *S. grosvenorii* and advances in their pharmacological activities within the last five years. Interestingly, available recent literatures revealed 20 new minor compounds with 7 metabolites that have been identified and characterized. Also, the reported advances in pharmacological activities of the *S. grosvenorii* phytochemicals on antidiabetic, anticancer, anti-inflammatory, antioxidant, anti-asthmatic, hepatoprotective, hypolipidemic and immunomodulatory effects, were discussed. In addition, new metabolites of mogrosides with potent effects were identified, and in some cases, the metabolites exhibited better activity than the parent compound. Besides, new insights on the molecular mechanisms of action, through which the phytochemicals mediate their bioactivities, were identified and discussed. Moreover, documented nutritional values and health advantages of *S. grosvenorii* were also highlighted, while suggestions for areas of further research and prospects were made.

**Keywords:** *Siraitia grosvenorii*; Mogrosides; Pharmacological Activities; Antidiabetics; Anticancer; Flavonoids

### Abbreviations

TCM: Traditional Chinese Medicine; LHG: Luo Han Guo; NMR: Nuclear Magnetic Resonance; DPPH: 2,2-diphenyl-1-picrylhydrazyl; MIC: Minimum Inhibitory Concentration; NF-kB: Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells; MGV: Mogroside V

### Introduction

The medicinal and nutritional benefits of *Siraitia grosvenorii* (Swingle) C. Jeffrey (Cucurbitaceae), also known as Monk Fruit or Luo Han Guo (LHG), have been widely utilized and reported for centuries, while more are presently being revealed. *S. grosvenorii*, is an herbaceous perennial plant with high medicinal values, originated from southern part of China, particularly Guangxi Province, and from northern Thailand. It has been used in Traditional Chinese Medicine (TCM) for more than 200 years. Reported folkloric or ethnomedicinal uses include: treatment of cough, arthritic pains, stomach ache, constipation, hyperglycemia or diabetes, cancer, allergy and infections such as sore throat [1,2]. Virtually every part of the plant is endowed with potent medicinal properties and bioactive compounds. Interestingly, its edible fruit also known as Luo Han Guo (LHG) contains a lot of phytochemicals, mainly cucurbitane glycosides or mogrosides, which confer high sweet taste to the fruit and its extracts [2,3]. Mogrosides are compounds containing mogrol and glycosylated sugar moieties joined by  $\beta$ -linkages [1]. The sweetness of mogrosides has been reported to be over 300 times sweeter than sucrose with minimal calorie content [4,5]. Nevertheless, mogroside II from unripe fruits of LHG possesses bitter taste possible due to high level un-saccharified

saponin glycosides [2]. The name Luo Han Guo simply refers to the fruit of *S. grosvenorii* and has often been used interchangeably as a synonym for the plant's common name. In some cases, *S. grosvenorii* has been referred to and known as *Siraitia fructus* [6]. In addition to the cucurbitane glycosides, other phytochemicals such as flavonoids, alkaloids, sterols and aliphatic acids have been the bedrock of the fruit's numerous pharmacological activities. It has been variously indicated that they possess antitussive, anti-oxidant, anti-diabetic, anti-cancer, anti-asthmatic, anti-bacteria, hepatoprotective, lipid lowering and immunomodulatory activities [2,7,8]. Over 100 phytochemicals have been isolated and characterized from the various parts of *S. grosvenorii*, particularly the fruits and the roots [6,7]. The prototype of these phytochemicals remains the cucurbitane glycosides known as the mogrosides isolated first in 1983 by Takemoto and co researchers [9]. Ever since then, a lot of compounds have been isolated from extract of *S. grosvenorii* or synthesized from biotransformation of mogrosides [3]. Previous reports on the review of *S. grosvenorii* chemistry and pharmacology have been documented, lastly in 2014 [5,7]. However, from 2014 till date more compounds both new, minor related compounds and their metabolites have been further characterized and reported. Therefore, the aim of this review is to highlight an overview of recently reported new minor compounds and their metabolites from *S. grosvenorii* within the last five years, including other compounds isolated before this period, but inadvertently omitted in the previous review works. In addition, this review will also provide an update overview of pharmacological activities of the *S. grosvenorii* phytochemicals, and their molecular mechanisms of action. From the online search, a total of about 40 recent publications were assessed and evaluated.

### Recent phytochemicals

Since the isolation of the first phytochemicals, mogrosides, thirty-five years ago from the fruits of *S. grosvenorii* [1,10], more compounds have been, and are still being, isolated and characterized with intriguing potent pharmacological activities. Also, from the roots and leaves of LHG many phytochemicals have been isolated and characterized [7,11]. Recently, more minor new compounds have been characterized, identified and reported either by natural isolation, metabolic and biotransformation processes of *S. grosvenorii* phytochemicals. These compounds were mainly cucurbitane glycosides, flavonoids and their metabolites.

### Cucurbitane glycosides and flavonoids

Many new cucurbitane glycosides or mogrosides from *S. grosvenorii* fruits were recently identified and reported. From a commercial aqueous alcoholic extract of LHG three new minor mogrosides were isolated by Prakash., *et al.* [12], while Li., *et al.* [13], also reported new mogrosides from fruits of *S. grosvenorii* using 1D, 2D-NMR and HR-ESI-MS techniques. In a separate study, among the 7 new cucurbitane glycosides isolated from the crude extract of *S. grosvenorii*, one has never been reported [14]. Furthermore, 12 new minor triterpenoids were identified by Zhou., *et al.* [6], using the ultra-high-performance liquid chromatography coupled with photo-iodide array and quadrupole/time-of-flight mass spectrometry (UPLC-PDA-QTOF-MS/MS) based on a multiple ion filtering (mPIF) strategy. In addition, 3 other compounds not hitherto highlighted in previous reviews; 7-oxo-mogrol, 5 $\alpha$ , 6 $\alpha$ -epoxymogrol and 25-dehydroxy-24-oxo-mogrol, were also identified in a study [10], while 4 new flavonols were isolated and characterized from the leaf, root and stem of *S. grosvenorii*, using HPLC-Q-TOF-MS screening technique [3]. These minor compounds, 20 in number, were shown in table 1.

### Metabolites of mogrosides

Several metabolites of mogrosides have been reported for the first time. New compound metabolites were identified from metabolism of siamenoside 1 when administered to rat *in vivo* [15]. Siamenoside 1 had been identified as the sweetest of the mogrosides with about 500 times sweeter than sucrose [10]. The metabolites were identified using high-performance liquid chromatography-electrospray ionization-ion trap-time of flight-multistage mass spectrometry (HPLC-ESI-IT-TOF-MS<sup>n</sup>) method [15], with differences in metabolites of ripe or saccharified and unripe fruits [16]. Furthermore, *in-vitro* biotransformation of mogroside V either by chemical conversion or enzymatic conversion with the help of powerful HPLC-ESI-IT-TOF-MS<sup>n</sup> technique, has yielded new potent metabolites and isomers of various mogrosides [17]. Also, biosynthesis of three new mogrosides have been reported via *in-vitro* enzymatic oxidation of cucurbitadienol [18]. Interestingly, pharmacological agents with potent active metabolites usually exhibit better and often additional activities due to the active metabolite(s). Such agents are usually referred to as pro-drugs, hence siamenoside 1 and other mogrosides with active metabolites may be referred to as probable pro-drugs or simply pro-mogrosides. Typically, metabolites of grosvenorine have exhibited better pharmacological activities than the parent compound [8]. Some of these metabolites, 7 in number, were listed in table 2.

Table 1: Recently identified minor cucurbitane glycosides.

| S/No | Chemical name                | Formula                                             | Plant part | Reference |
|------|------------------------------|-----------------------------------------------------|------------|-----------|
| 1    | 11-deoxymogroside V          | C <sub>60</sub> H <sub>102</sub> O <sub>28</sub>    | Fruit      | 12        |
| 2    | 11-deoxyisomogroside V       | C <sub>60</sub> H <sub>102</sub> O <sub>28</sub> Na | Fruit      | 12        |
| 3    | 11-deoxymogroside VI         | C <sub>66</sub> H <sub>113</sub> O <sub>33</sub>    | Fruit      | 12        |
| 4    | 11-oxoisomogroside V         | C <sub>60</sub> H <sub>100</sub> O <sub>29</sub>    | Fruit      | 14        |
| 5    | Di-hydroxyl-mogroside V      | C <sub>60</sub> H <sub>102</sub> O <sub>31</sub>    | Fruit      | 6         |
| 6    | 7-O-mogroxide IV             | C <sub>61</sub> H <sub>104</sub> O <sub>33</sub>    | Fruit      | 6         |
| 7    | Hydroxyl-mogroside IV        | C <sub>55</sub> H <sub>92</sub> O <sub>27</sub>     | Fruit      | 6         |
| 8    | 11-O-mogroside VI            | C <sub>55</sub> H <sub>94</sub> O <sub>27</sub>     | Fruit      | 6         |
| 9    | Di-hydroxyl-mogroside IV     | C <sub>54</sub> H <sub>92</sub> O <sub>26</sub>     | Fruit      | 6         |
| 10   | 7-O-mogroside III            | C <sub>54</sub> H <sub>94</sub> O <sub>28</sub>     | Fruit      | 6         |
| 11   | Di-hydroxyl-mogroside III    | C <sub>49</sub> H <sub>82</sub> O <sub>22</sub>     | Fruit      | 6         |
| 12   | Hydroxyl-mogroside V         | C <sub>49</sub> H <sub>84</sub> O <sub>23</sub>     | Fruit      | 6         |
| 13   | Hydroxyl-mogroside III       | C <sub>61</sub> H <sub>104</sub> O <sub>30</sub>    | Fruit      | 6         |
| 14   | 11-Deoxymogroside IV         | C <sub>49</sub> H <sub>84</sub> O <sub>21</sub>     | Fruit      | 6         |
| 15   | Dehydration-mogroside II     | C <sub>43</sub> H <sub>72</sub> O <sub>16</sub>     | Fruit      | 6         |
| 16   | Di-dehydration-mogroside III | C <sub>48</sub> H <sub>78</sub> O <sub>17</sub>     | Fruit      | 6         |
| 17   | Iso-mogroside IVe            | C <sub>54</sub> H <sub>92</sub> O <sub>24</sub>     | Fruit      | 18        |
| 18   | 11-epi-mogroside V           | C <sub>60</sub> H <sub>102</sub> O <sub>29</sub>    | Fruit      | 18        |
| 19   | 11-oxo-siamesoside I         | C <sub>54</sub> H <sub>90</sub> O <sub>24</sub>     | Fruit      | 13        |
| 20   | 11-oxo-mogroside VI          | C <sub>66</sub> H <sub>110</sub> O <sub>34</sub>    | Fruit      | 13        |

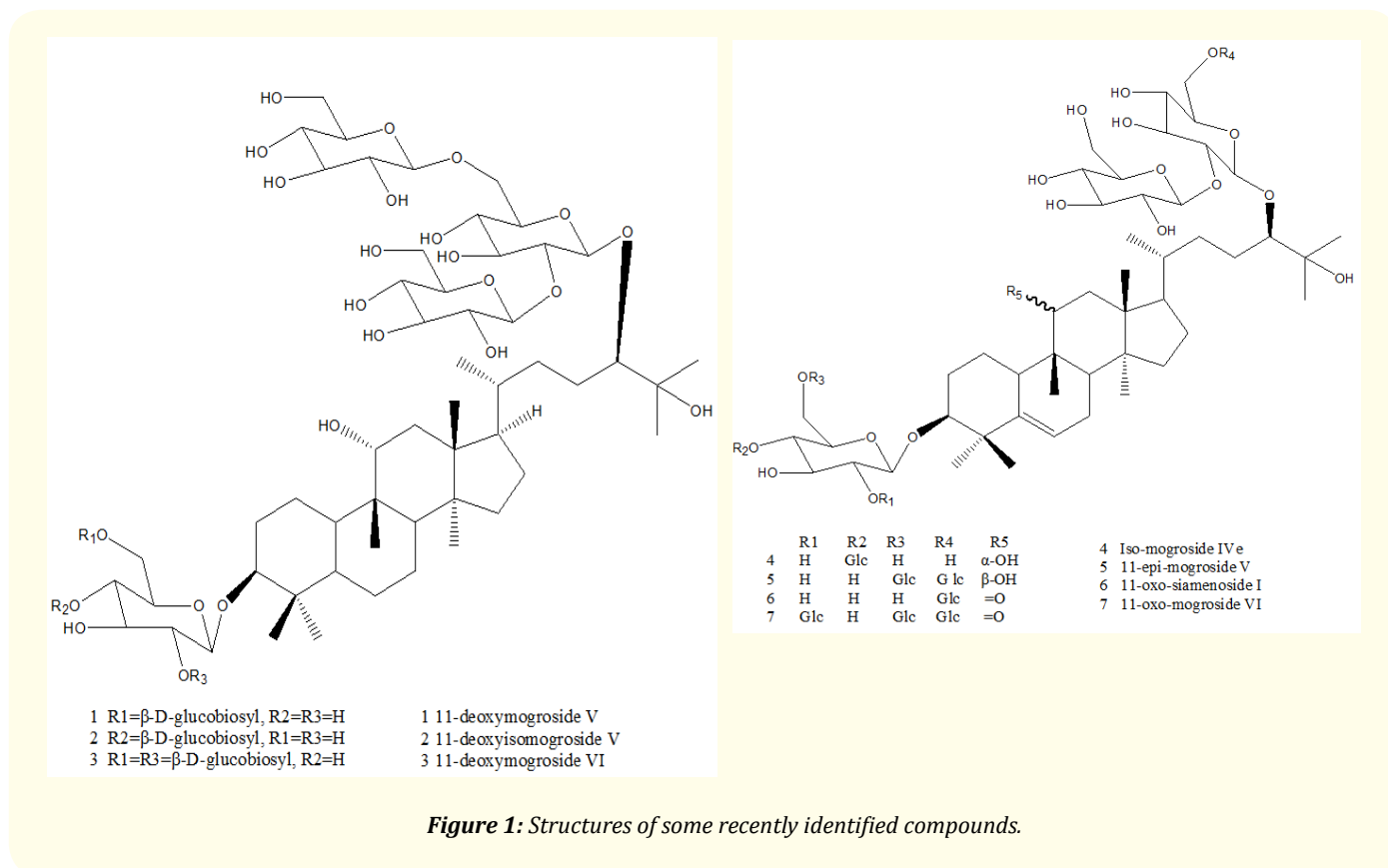


Figure 1: Structures of some recently identified compounds.

**Table 2:** Recently identified cucurbitane glycosides' metabolites.

| S/No | Chemical name                           | Formula                                          | Parent mogroside | Reference |
|------|-----------------------------------------|--------------------------------------------------|------------------|-----------|
| 1    | Dehydrogenated mogrol                   | C <sub>30</sub> H <sub>50</sub> O <sub>4</sub>   | Siamenoside I    | 16        |
| 2    | Dihydroxylated mogrol                   | C <sub>30</sub> H <sub>52</sub> O <sub>6</sub>   | Siamenoside I    | 16        |
| 3    | Didehydrogenated trihydroxylated mogrol | C <sub>30</sub> H <sub>48</sub> O <sub>7</sub>   | Siamenoside I    | 16        |
| 4    | Mogroside VI isomer                     | C <sub>66</sub> H <sub>112</sub> O <sub>34</sub> | Mogroside V      | 18        |
| 5    | Mogroside II isomer                     | C <sub>42</sub> H <sub>72</sub> O <sub>14</sub>  | Mogroside V      | 18        |
| 6    | Monoglycosylated mogrol                 | C <sub>36</sub> H <sub>62</sub> O <sub>9</sub>   | Mogroside V      | 18        |
| 7    | 11-oxo-24,25-epoxyl cucurbitadienol     | C <sub>30</sub> H <sub>48</sub> O <sub>3</sub>   | Cucurbitadienol  | 19        |

### Pharmacological activities and mechanisms of action

Various pharmacological activities associated with bioactive compounds from *Siraitia grosvenorii* fruits and other parts of the plant have been reported [5,7]. The cucurbitane glycosides called mogrosides and flavonoids have been identified as the major phytochemicals responsible for these biological activities [3,4]. The pharmacological activities and other health benefits of *S. grosvenorii* include anti-tussive, anti-asthmatic, antidiabetic, antihyperlipidemic, anticancer, antifibrotic, antiaging, hepatoprotective, antimicrobial and immunomodulatory effects. The probable mechanisms of action by which these activities are being mediated have been determined, while recent reports revealed more molecular mechanisms

#### Antitussive and anti-asthmatic effects

In Traditional Chinese Medicine (TCM) *S. grosvenorii* fruit has been used for its potent antitussive and expectorant effects [7], hence the use in treatment of cough and other respiratory disorders such as asthma, acute lung injury and pulmonary fibrosis. The cucurbitane glycosides, particularly mogrosides III E and V have exhibited anti-inflammatory effects in mice [19,20]. The anti-inflammatory activity of LHG extract and its mogrosides might be contributing to its antitussive and expectorant action. Asthma and other respiratory system disorders owe their pathogenesis to inflammation of smooth muscle cells lining the air passages. The resultant effects of these are chronic obstruction of air passages leading to dyspnoea, coughing and wheezing mediated by release of certain allergens and inflammatory mediators such as cytokines, serotonin and histamine from the mast cells. Recent report showed that mogrosides exhibited protective effect against pulmonary fibrosis through the inhibition of fibroblast activation and collagen deposition regulated by toll-like receptor 4 (TLR4) pathways [20]. Hence, mogrosides can be referred to as TLR4-receptor agonists. On the other hand, the anti-inflammatory mechanisms of mogrosides might be probably be due to inhibition of release of histamine and pro-inflammatory cytokines, blockade of cyclooxygenase-2 (COX-2) action and attenuation of the NF-κB signalling pathway [19]. *S. grosvenorii* fruits also exhibited significant inhibition of histamine-induced nasal rubbing and histamine-induced triple action on mice skin. These activities usually will lead to down regulation of inflammatory processes in the lungs relieving nasal congestion, allergy and dyspnoea.

#### Anti-diabetic effect

Diabetes Mellitus (DM) is one of the metabolic disorders currently getting to an epidemic prevalence globally. Various reports have shown that both extract and mogrosides from LHG exhibited anti-hyperglycemic or anti-diabetic effect by reducing post-prandial blood glucose level and improving insulin resistance [4,7]. Apart from hyperglycaemia, insulin resistance is a major hallmark of DM pathogenesis, particularly Type II DM and this can be modulated by the extracts and mogrosides of Monk Fruit. Interestingly, the inhibition of the intestinal brush border maltase enzyme was considered as the possible mechanism of this anti-hyperglycemic effect [4]. However, recently the glucose mobilization and uptake by cells, as was reported by Li., *et al.* [13], where mogrosides showed potent glucose uptake by the HepG2 cells *in vitro*, was indicated as another possible mechanism of action. Increased glucose uptake and mobilization by skeletal muscles and adipose tissues has been the mechanism of anti-hyperglycemic action of some standard antidiabetic agents such as biguanides, example is metformin. On the other hand, biguanides are insulin secretagogue highly recommended for obese patients since they also affect the adipocytes. This is in corroboration with pharmacological activities of mogrosides and other triterpenoid saponins that have exhibited both antidiabetic and anti-hyperlipidemic activities [21,22]. Furthermore, mogrosides (mostly mogroside V) can be regarded as insulin secretagogues and have exhibited significant insulin stimulatory effect on the beta cells of the pancreas [5]. In a recent related study, mogrosides exhibited antidiabetic effect via modulation of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), that plays an important physiological role in energy homeostasis [14]. Another possible mechanism of mogroside antidiabetic effect is the scavenging effect on reactive oxygen species (ROS), that are responsible for the pancreatic beta cell apoptosis, and their interference

with oxidative stress-induced FOXO1 activation [23]. In the adipocytes, PGC-1 $\alpha$  regulates adipocyte differentiation, lipid metabolism and insulin sensitization with possibility of limiting atherosclerosis and diabetes complications. Antidiabetic standard agents, thiazolidinediones, such as rosiglitazone and pioglitazone are PGC-1 $\alpha$  agonists, hence are known as insulin sensitizers. Therefore, mogrosides and their metabolites, that exhibited modulatory activity on the PGC-1 $\alpha$ , can be referred to as insulin sensitizers' related agents. However, more studies are recommended in this regard to ascertain the specific mechanisms of mogrosides with respect to their agonistic effect on this receptor, and their general anti-diabetic action.

#### Anti-cancer effect

Recent surge in cancer related deaths worldwide has necessitated the need for new and alternative therapeutic measures in countering the epidemic. Screening of medicinal plants' extracts and their phytochemicals for anticancer activities has recorded a boost towards revelation of novel and potent anticancer compounds. Extracts and compounds isolated from *S. grosvenorii* are not left out in this regard. The cucurbitane-glycoside natural sweeteners or mogrosides have demonstrated anticancer effects in previous reports [5,7]. However, recent reports showed that mogroside V inhibited proliferation and survival of pancreatic cancer cells [24], while mogroside IVe exhibited anticancer effects against colorectal cancer HT29 cells and throat cancer Hep-2 cells [25]. In addition, mogrol, a metabolite of mogrosides, has demonstrated anticancer activities against human leukemia cell line (K562) via induction of apoptosis and cell cycle arrest [26]. These recent works of Liu and co-workers have again brought to fore the anticancer potentials of mogrosides and their metabolites [24,26]. The specific mechanisms through which mogrosides mediate their anticancer activities may not have been adequately elucidated by the present studies. However, inhibition of aryl hydrocarbon receptor (Ahr)-mediated signal transduction [7], blockade of the downstream targets of the STAT3 pathway that promote cell proliferation [24], enhanced expression or upregulation tumour protein p53 that induces tumour cell apoptosis, and suppression of matrix metalloproteinase 9 enzyme (MMP-9) expression via inhibition of ERK1/2 phosphorylation-dependent activation [25], are some of the currently documented mechanisms. Therefore, more studies are being expected with respect to the mechanisms of anticancer activities of mogrosides of LHG.

#### Anti-oxidant and anti-aging effects

Oxidative stress has been identified as a major pathogenic event associated with many diseases, ranging from metabolic to proliferative disorders such as diabetes mellitus, coronary heart diseases, stroke, degenerative diseases, cancer, aging and inflammation of various kinds [27,28]. Factors responsible for oxidative disorders are reactive free radicals (RFR) and reactive oxygen species (ROS), that are generated by several biochemical reactions in the body especially when they are not effectively scavenged by the cellular processes [29]. Phytochemicals, mostly phenolic compounds such as polyphenols, flavonoids and terpenoids, have exhibited potent antioxidant activities due to their ability to transfer electrons to ROS and maintain redox homeostasis. Terpenoids and flavonoids are major phytochemicals found in LHG, while terpenoids make up the cucurbitane natural sweeteners or mogrosides, flavonoids consist of flavonols and organic acids [7]. Reports showed that *in-vitro* antioxidant activities of mogroside V and 11-oxo-mogroside V showed significant scavenging or inhibitory effects on reactive oxygen species responsible for DNA damage [5], while kaempferol-3,7-O- $\alpha$ -L-Dirhamnopyranoside, a flavonoid from the leaves of *S. grosvenorii*, exhibited potent radical scavenging activity with an IC<sub>50</sub> value of 3.97 mg/ml [30]. Recently, mixed saponin product (MSP, mogrosides II and III) and mogroside V, separately showed potent antioxidant or scavenging activity against DPPH free radicals with an IC<sub>50</sub> values of 0.954 and 0.433 mg/ml, respectively [2]. Among several hypothesis regarding the pathogenesis of aging, one that is recently receiving tremendous attention is the effect of mitochondrial generated reactive oxygen species (ROS). Enhanced generation of ROS by mitochondria, the power house of the cell, causes oxidative stress leading to mitochondrial dysfunction and excitotoxicity, DNA mutation, increased cellular inflammation, rapid breakdown of tissues and eventual degeneration of body cells known as rapid aging [31,32]. Age related disorders such as Alzheimer's and Parkinson's diseases, are due to rapid aging because of increased cellular oxidative stress and inadequate activities of endogenous and exogenous antioxidants in the body [32]. Therefore, by their antioxidant properties, mogrosides and their metabolites can contribute in keeping the ROS in check, thereby enhancing longevity. However, further research is encouraged in this regard to determine the possible mechanisms of antioxidant effects of mogrosides.

### Hepatoprotective effect

Hepatoprotective activities of extracts and mogrosides of *S. grosvenorii* have been reported, with both the extract and mogrosides showing significant protection of mice liver from carbon tetrachloride (CCl<sub>4</sub>)-induced acute liver toxicity [7]. Recently, Cao, et al. reported that mogroside IVE significantly attenuated CCl<sub>4</sub>-induced liver fibrosis and for the first time and was able to assess the possible mechanism of hepatoprotective effect [33]. Eight weeks treatment with mogroside IVE significantly protected the hepatocytes and improved liver function by inhibition of inflammatory cytokines such as TGF $\beta$ , IL-1 and IL-6. Also, on the molecular level, mogroside IVE mediated hepatoprotective effect by inhibiting the toll-like receptor 4 (TLR4) and the hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) signalling pathways [33], making it a potential agent for treatment of liver fibrosis. Furthermore, the down regulation of the TLR4 pathway has also been reported as one of the possible anti-inflammatory vis-a-vis hepatoprotective mechanisms of mogrosides [20].

### Anti-microbial effect

Anti-microbial activities of extract and compounds from *S. grosvenorii* have been variously reported [7,11]. Among the five flavonoids isolated from the leaves of LHG, aloe emodin exhibited the most potent antimicrobial activities against tested bacteria and fungi which are *Streptococcus mutants*, *Actinobacillus actinomycetemcomitans*, *Fusobacterium nucleatum* and *Candida albicans* with an MIC values of 1.22, 6.10, 12.20 and 6.10  $\mu$ g/ml, respectively [11]. However, the mechanisms of antibacterial and antifungal activities are yet to be reported, with more studies being expected on antimicrobial properties of mogrosides and their metabolites, especially now that the scientific world is in dire need of novel or new antibacterial molecules.

### Hypolipidemic effect

Dyslipidaemia, excessive accumulation of lipids in the blood, is one of the major global metabolic disorders currently on the increase with its attendant complications such as cardiovascular diseases, diabetes with insulin resistance and obesity. A recent report showed that mogrosides and their metabolites from *S. grosvenorii*, exhibited anti-obesity activities by suppressing adipogenesis pathways [21], and for the first time, this review is reporting this mogroside activity. Among the bioactive classes of phytochemicals, polyphenols and saponins possess hypolipidemic, hypocholesterolemic and hypoglycaemic activities, helping to modulate obesity and related disorders [22]. Similarly, these activities can also be ascribable to mogrosides and their metabolites. Mogrol, an aglycone of mogroside from *S. grosvenorii*, suppressed the differentiation of preadipocytes to adipocytes. This is in contrast with its glycosides, mogrosides, as mogrol is the major circulating form in the blood after the removal of the glucose residue in the gut [21]. The suppression of cAMP response element-binding protein (CREB) phosphorylation and CRE-mediated transcription in the initial stage of differentiation, and by activation of the AMPK signalling pathways at the both the early and late stages, are the proposed mechanisms by which mogrol suppresses lipid accumulation in 3T3-Li adipocytes cells [21]. Additionally, activation of PPAR activities in the adipocytes, inhibition of low-density lipoprotein (LDL) oxidation, and inhibitory effect on lipid peroxidation, were other reported mechanisms concerning mogrosides' hypolipidemic action [14,34]. In overall, these processes cause decrease in lipid accumulation, reduce atherogenic potentials of LDL, modulate obesity and prevent cardiovascular events as well as diabetes, although more studies are expected.

### Immunomodulatory effect

Mogroside V when administered to mice showed immunostimulatory effect [35], and this is the first time this activity of mogrosides of *S. grosvenorii* is being reported in a review. Several reports have shown the inter-relationship between immunomodulation, anti-inflammatory, antioxidant and anticancer activities of polyphenolic compounds from medicinal plants [36-38]. Modulation of the immune system and the suppression of pro-inflammatory mediators are among the proposed mechanisms of antioxidant and anti-cancer activities of polyphenols [29,36]. Furthermore, the anti-cancer, antioxidant and anti-inflammatory activities of extracts and mogrosides of *S. grosvenorii*, which are highly phenolic in nature, have been established and reported [19,25]. Hence extracts and mogrosides together with their metabolites are good candidates for boosting the immune system and could also be a welcome adjuvant in immunotherapy of various diseases affecting the immune system, particularly viral infections. The mechanisms through which mogrosides mediates its immunostimulatory action were up-regulation of both the CD4 T-lymphocytes and anti-inflammatory cytokines as well as downregulation of pro-inflammatory cytokines [35]. On the other hand, the established agonistic effect of mogrosides on TLR4-receptors showed their immune stimulant properties [20]. Therefore, more studies are expected on the immunomodulatory activities of mogrosides as well as the determination of the possible specific mechanisms of their immune related actions.

### Pharmacokinetic profile

Mogrosides when administered to rats orally and parenterally have shown good absorption and distribution with plasma identification of their metabolites [10]. Recent studies showed an excellent identification of metabolites of mogroside V (MGV) in the plasma follow-

ing its oral and intravenous administration in both mice and rats, an indication that MGV pharmacological activities could likely be due to its active metabolites [10,39,40]. Hence MGV can be referred to as a pharmacologically active pro-drug. Metabolites of mogroside V identified in the plasma after administration in laboratory animals include, mogrol and mogroside II, exhibited better potent pharmacological (anti-diabetic) activity [39,40]. Comparatively, MGV showed poor oral availability when compared to intravenous administration (iv), with an estimated 8.73% bioavailability, while elimination half-life ( $t_{1/2}$ ) for MGV metabolite after oral and iv administrations were 2.46h and 1.53h, respectively [39]. Hence mogrosides showed excellent tissue distribution since the metabolites can be traced to various organs such as the heart, liver, spleen and lungs when administered in rats [10]. Metabolism of mogrosides has been shown to be via both Phase I and Phase II drug metabolizing pathways, particularly Phase I, that involves hydrolysis and oxidation reactions to yield polar active metabolites, such as mogrol, mogrosides II and III [10]. Also, the conversion of MGV by the human and rats' intestinal enzymes to mogroside IIA, mogroside IIIE and mogrol, has been revealed with the help of powerful HPLC-ESI-IT-TOF-MSn chromatographic technique [10,17]. On elimination, MGV can be extensively excreted from the body through biliary route via active transport [40]. However, more studies are required for more understanding of the detail pharmacokinetic profile of mogrosides and other phytochemicals of *S. grosvenorii*.

### Toxicological profile

Since the extract from the *S. grosvenorii* have been used in TCM for hundreds of years as food and medicinal agent, one can simply infer and ascribe to them good toxicological profile. However, there is the need to scientifically ascertain this assumption exploring relevant animal (*in vivo*) and cellular (*in vitro*) reported studies. The extract of *S. grosvenorii* has shown to be safe when administered to mice with the maximum tolerated dose greater than 100 g/kg, an indication of good safety profile [7]. Similarly, recent toxicity studies on mogroside V and a mixed saponin product (MSP) from *S. grosvenorii* showed a good safety profile after 7-day administration with no lethality or toxicity in mice [2]. The serum biochemical parameters showed no significant difference between the treated and control groups. Also, no change in the body and organ weights, as well as morphology of both treated and control animals [2]. This corroborated with the previously reported work where four weeks administration of mogrosides in dogs showed no significant change in hematologic parameters and organs morphology [7]. Moreover, an  $LD_{50}$  of mogroside in mice has been estimated to be greater than 10,000 mg/kg, indicating a high safety margin [7]. Nevertheless, more toxicity tests are expected to be performed especially with the recently isolated cucurbitane glycosides and their metabolites.

### Future Prospects

Expectantly, one of the areas of future research in *S. grosvenorii*, points towards synthesis of new drug molecules from the isolated phytochemicals, and this could be very interesting to phyto-chemists and pharmacologists. Modification of functional groups and screening of resultant compounds for pharmacological activities could lead to new drug discovery, which is hereby encouraged. The numerous pharmacological activities of compounds of LHG necessitate the need to facilitate improved yield of the phytochemicals with better bioactivity. However, the difficulty to synthesize and purify mogrosides, due to their complex molecular structure, has been identified [10] and efforts are being made towards surmounting this through several approaches. Reports indicated the discovery of new functional genes with improved genome assembly that has been identified by Xia and co-workers [41], which could be a prelude towards improved bioactive phytochemicals. Similarly, recent reports on gene expression [42] and gene characterization [43], of the two key enzymes, squalene synthase (SQS) and cycloartenol synthase (CAS), responsible for biosynthesis of triterpenoids and steroids in *S. grosvenorii* revealed the hope for gene expression and approach to engineer the effective biosynthesis of cucurbitane triterpenoids with better potent pharmacological activities.

### Nutritional value

Nutritional value of Monk Fruit is as old as its medicinal usefulness. Natural sweeteners, cucurbitane glycosides, from the fruits have been commercialized and used as a substitute to sugar and sugar-alternatives in meals, especially among diabetic patients. A typical health benefit to curtail or restrict the rate of sugar consumption and its alternatives such as aspartame that have health implications. The *Siraitia grosvenorii* fruit extract (SGFE) containing mogrosides has been approved by the US Food and Drug Administration (FDA) to be used as a safe natural sweetener, and they contain very few or no caloric content. Depending on the mogroside's content, SGFE may be 100 to 250 times sweeter than sugar [10]. Presently, SGFE juice concentrate is being used in the production of beverages and food formulas, helping to moderate caloric content, an opportunity for food industries not to overlook.

## Conclusion

*Siraitia grosvenorii* or Monk Fruit (LHG) is an amazing medicinal and nutritional plant with an array of isolated phytochemicals possessing appealing pharmacological activities. Reports on the *S. grosvenorii* phytochemicals and their pharmacological activities have been quite exciting and hopefully more interesting discoveries are on the way with expected further research. Since polyphenols are majorly responsible for most of the activities, targets on both synthesis and pharmacological activities of these compounds needs to be focused on drug discovery. Finally, patients on treatment of diseases such as diabetes, asthma and rheumatoid arthritis, should be encouraged to add monk fruit extract to their diet as an adjuvant to boost the therapeutic effects of standard agents. This is more so, owing to the lack of any significant traceable toxicity to LHG for now, and the current support of World Health Organisation (WHO) on the combination use of medicinal plants with standard agents for potent synergistic effects.

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## Author Disclosure Statement

No competing financial interests exists.

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