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Development of Natural Product Innovation Based on the Bio-Circular- Green (BCG) Economy Model

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ABSTRACT

Currently, global trends in the development of natural product innovations are not only based on their novelties and feasibility for commercialization but also on comprehensively addressing environmental challenges for the planet's sustainability. In this regard, the concept of a BCG (Bio/Circular/Green) economy has been introduced as a promising strategy where a holistic economy integrated with research-based innovation are applied to make the value added of native natural and cultural resources, reduce waste, preserve and restore the ecosystems. Based on the BCG model, various health production innovations made from native plants have been developed through green microwave extraction using alternative green solvents. For example, [6]-gingerol pastilles for motion sickness and *Garcinia cowa* leaf extract containing chamuangone.

KEYWORDS
Chamuangone; [6]-Gingerol; Ginger; *Garcinia cowa*; Green extraction; Green solvent; Microwave

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Introduction

Currently, global trends in the development of natural product innovations are not only based on their novelties and feasibility for commercialization but also on comprehensively addressing environmental challenges for the planet's sustainability. Since the Asia-Pacific Economic Cooperation (APEC) 2022 meeting in Bangkok, Thailand, the concept of a BCG economy has been introduced as a promising strategy where a holistic economy integrated with research-based innovation are applied to make the value added of native natural and cultural resources, reduce waste, preserve and restore the ecosystems to build a prosperous and sustainable economic system (Figure 1). The BCG model emphasizes applying science, technology, research, and innovation to turn Thailand's advantage in natural enrichment and unique traditional cultures into a competitive advantage, as well as promoting sustainability of biological and cultural resources, society, and the environment.

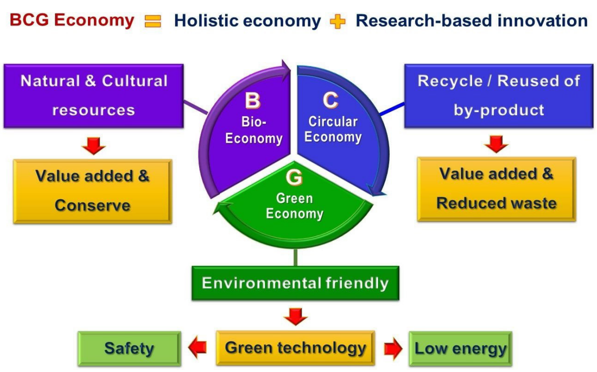

Figure 1. BCG economy model.

Based on the BCG model, various health production innovations made from native plants have been developed through green microwave extraction using alternative green solvents. In this regard, the three concepts of green extraction have been applied, including 1) short-time and low-energy extraction methods; 2) green and reusable solvents; and 3) high-quality (high-level of active compound) extracts. Most conventional heating extract methods, such as reflux and Soxhlet extractions, are process-expensive in terms of time and energy. In contrast, microwave extraction has been approved as a green extraction method because it consumes markedly less energy and time and produces high-quality herbal extracts. Thus, microwave extraction may reduce the cost of production due to its lower energy and time consumption [1,2]. Furthermore, various organic solvents that are usually used in most natural product research and development, especially in the extraction process, e.g., methanol, acetone, ethyl acetate, chloroform, ether, dichloromethane, petroleum ether, and hexane, etc., are hazardous and volatile. Thai FDA (Food and Drug Administration) do not allow the use of these organic solvents for industrial production of herbal products. Therefore, the innovative extractions are focused on a green extraction that is friendly to the environment and humans and reduces production costs. Various alternative green solvents, such as the pharmaceutical excipients in pastilles and agro-solvents from agricultural resources, including ethanol, vegetable oils, glycerol, D-limonene, and α-pinene, have been successfully used for the development of nutraceuticals and functional foods using green microwave extraction. Some examples of herbal innovations that have been developed based on the BCG model are described as follows.

Ginger (*Zingiber officinale*) is a widely recognized spice that holds a rich history of traditional medicinal use across various Asian countries. It is an integral component of the traditional medicine system to address a broad spectrum of

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health issues, including flatulence, nausea, vomiting, muscle pain, and osteoarthritis. Indeed, various meta-analyses and systematic reviews have demonstrated sufficient evidence to support the effectiveness of ginger powders in alleviating the symptoms of nausea and vomiting resulting from pregnancy, motion sickness, chemotherapy, and postoperative cases. However, it is crucial to note that conflicting results in some clinical studies may stem from variations in the quality and standardization of ginger products used in the research. [6]-Gingerol, a major bio-active compound in ginger, exhibits diverse pharmacological properties, including anti-nausea and vomiting, antioxidant, anti-inflammatory, antiviral, antitumor, and anticancer effects. Its anti-emetic capabilities have been linked to interactions with serotonin (5-HT_3) and muscarinic (M_3) receptors [3].

Currently, 5-HT_3 receptor antagonists such as dolasetron, granisetron, and ondansetron are the established standard therapy to treat or prevent nausea and vomiting. Nevertheless, ongoing research is exploring alternative approaches, like [6]-gingerol derived from ginger. This exploration suggests the potential for complementary or alternative antiemetic strategies, to address the unique needs of individual patients with improved efficacy and safety. In recent developments, a green microwave-assisted extraction (MAE) utilizing alternative green solvents has proven to be an efficient method for extracting [6]-gingerol. Two distinct [6]-gingerol extracts were prepared through MAE, employing green solvents derived from pharmaceutical excipients used in a pastille formula; specifically, (1) glycerol and (2) a eutectic mixture of citric acid and sucrose [4]. These extracts were then evaluated for their *ex vivo* effects on ileal contractions via 5-HT_3 and M_3 receptors, as well as lower esophageal sphincter (LES) contraction, in comparison to pure [6]-gingerol. High-performance liquid chromatography (HPLC) analysis revealed that both [6]-gingerol extracts from glycerol (GE) and the eutectic mixture of citric acid and sucrose (EME) contained the same [6]-gingerol content of 1.7% w/w. Notably, [6]-gingerol, GE, and EME demonstrated significant inhibition of ileal contraction via M_3 and 5-HT_3 receptors in a dose-dependent and noncompetitive manner. However, only [6]-gingerol and EME exhibited a tendency to stimulate LES tone. These findings underscore the potential of GE and EME as potent nutraceuticals to prevent nausea and vomiting, showcasing the promise of green extraction methods in enhancing the therapeutic applications of [6]-gingerol [5].

Garcinia cowa, known as "Chamuang" in Thai, serves a dual purpose as its leaves are not only a culinary ingredient in dishes like "Moo-Chamuang" but also play a vital role in the Thai traditional medicine system. The leaves contain chamuangone, a notable polyprenylated benzophenone derivative, which serves as a major bioactive component. Chamuangone exhibits a range of biological activities, including anti-cancer and antimicrobial effects, highlighting the plant's potential contributions to both health and cuisine. Chamuangone has been reported to deliver strong cytotoxic effects against K562 and K562/ADM leukemia (IC_{50} values of 3.8 and 2.2 μM, respectively), SBC_3 and A549 human lung adenocarcinoma (IC_{50} values of 6.5 and 7.5 μM, respectively), HT-29 human colorectal adenocarcinoma (IC_{50} value of 0.04 μM), and MCF-7 human breast adenocarcinoma (IC_{50} value of 4.0 μM) cell lines [6]. Furthermore, chamuangone exerted a potent inhibitory effect on the proliferation and migration of HeLa human cervical tumor cells [7]. Additionally, it also induced apoptotic cell death through a profound inhibition of tyrosine kinase, with an IC_{50} value of 2.8 nM, targeting the epidermal growth factor receptor (EGFR). These findings underscore the potential of chamuangone as a bioactive compound with anti-cancer properties, shedding light on its role in future therapeutic applications.

Similarly, chamuangone showcased noteworthy pharmacological activities beyond its anticancer effects. This bioactive compound demonstrated potent leishmanicidal activity against *Leishmania major*, with an IC_{50} value of 10.7 μM [6]. Additionally, chamuangone displayed potent antibacterial properties, inhibiting the growth of *Helicobacter pylori* and *Streptococcus viridans* with an MIC value of 31.0 μM. It also delivered antibacterial effects against *S. pyogenes* (MIC value of 15.5 μM), as well as *Enterococcus* sp., *Bacillus subtilis*, and *Staphylococcus aureus* (MIC value of 62.0 μM) [8]. These diverse activities highlight chamuangone's potential in addressing various health-related challenges, highlighting its significance in anticancer and antimicrobial therapy.

Additionally, a quantitative HPLC method has been established for measuring chamuangone content in extracts, facilitating the evaluation of appropriate solvents for its extraction. The study identified hexane as the most suitable solvent for chamuangone extraction, attributed to its comparable non-polar properties to that of chamuangone [6]. However, the use of hexane is restricted for nutraceutical applications due to its toxic and volatile nature. Recently, an optimized MAE method has been introduced, utilizing rice bran oil as an alternative green solvent for the preparation of a standardized chamuangone extract from *G. cowa* leaves. This method aims to provide a high-quality extract, demonstrating its potential for commercialization in the production of functional foods. By utilizing rice bran oil as a green solvent, this approach meets the criteria of sustainable practices and paves the way for eco-friendly extraction methods in the development of bioactive compounds for commercial applications [9]. The standardized extract, containing chamuangone at 0.2% w/v, underwent *in vitro* cytotoxic evaluation against various cancer and normal cell lines. The findings demonstrated its notable anticancer properties, particularly against HT-29, MCF-7, and A549 cell lines, with the IC_{50} values of 12.8, 16.0, and 15.3 μg/mL, respectively. Importantly, the extract exhibited no toxicity towards human gingival fibroblasts, indicating a selective cytotoxic effect on cancer cells while sparing the normal cells. These results underscore the potential therapeutic value of the chamuangone-containing extract in the development of anticancer agents.

Disclosure statement

The author declared that they have no conflict of interest.

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