THE ELUCIDATION OF UNDERLYING MECHANISMS ASSOCIATED WITH NEUROPROTECTIVE EFFECTS OF SELECTED PLANT-DERIVED FUNCTION INGREDIENTS IN *CAENORHABDITIS ELEGANS*

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MASTER OF SCIENCE
IN
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Degree	Master of Science (Health and Biomedical Analytics)
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ABSTRACT

Neurodegenerative diseases, such as Parkinson's disease (PD) are characterized by a progressive decline in nervous system function. These conditions are becoming increasingly prevalent worldwide, including in Thailand, primarily due to age-related degeneration and limited treatment options. Reducing oxidative stress is a promising approach to prevent and slow disease progression, with plant-based antioxidants showing significant potential. This study evaluated the antioxidant potential of medicinal plants approved by the Thai Food and Drug Administration (FDA), focusing on microencapsules containing a standardized extract of *Curcuma longa* L. *Caenorhabditis elegans* (*C. elegans*) was used as a model organism to investigate the neuroprotective mechanism of curcumin microencapsulated against 6-hydroxydopamine (6-OHDA)-induced dopaminergic (DA) neurodegeneration, and their applicability in the food industry was tested by incorporating them into ready-to-eat extruded snacks. The results showed that *Curcuma longa* is a locally medicinal plant that has demonstrated a strong neuroprotective effect and a good antioxidant capacity in a systematic review. It also high levels of phenolic and flavonoid compounds, exhibiting strong antioxidant activity through various mechanisms. Microencapsulation (sCL11064) preserved these properties without toxicity, as the sCL11064 did not effects on feeding behavior test, although there are still limitations in concentrations that have not yet shown positive findings, it demonstrated neuroprotective effects

against neurodegeneration in dopamine neurons induced by 6-OHDA. Additionally, functional foods made from unripe banana flour and fortified with sCL11064 represent a novel product with high consumer acceptance. These results highlight the potential of antioxidant-enriched functional foods for promoting neurological health. However, further study is required to determine its *in vivo* antioxidant efficacy, including superoxide dismutase (SOD), catalase (CAT), and malondialdehyde (MDA) levels, as well as neuroprotective testing in rodent models and clinical trials.

Keywords: *Curcuma longa* L., Microencapsulation, Antioxidant Activity, Neuroprotective Effect, Parkinson's Disease, *Caenorhabditis elegans*

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ABBREVIATIONS AND SYMBOLS

ABTS	2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
BDMC	Bisdemethoxycurcumin
C. elegans	*Caenorhabditis elegans*
CAT	Catalase
D. melanogaster	*Drosophila melanogaster*
DAT-1	Dopamine Transporter Gene
DMC	Demethoxycurcumin
DPPH	2,2-diphenyl-1-picrylhydrazyl (DPPH) assay
E. coli	*Escherichia coli*
EDTA	Ethylenediaminetetraacetic Acid
FDA	Food and Drug Administration
FRAP	Ferric Reducing Antioxidant Power
GA	Gum Arabic
GBD	Global Borden of Disease
HCI	Hydrochloric Acid
HD	Huntington's Disease
HPLC	High-Performance Liquid Chromatography
IC_{50}	Half Maximal Inhibitory Concentration
LB	Lewy Body
LRRK2	Leucine-rich repeat kinase 2
MCA	Metal Chelating Assay
MD	Maltodextrin
MDA	Malondialdehyde
MMP	Mitochondrial Membrane Potential

ABBREVIATIONS AND SYMBOLS

MPP+	1-methyl-4-phenylpridinium ions
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NBT	Nitroblue Tetrazolium
NGM	Nematode Growth Medium
Nrf2	Nuclear Factor Erythroid 2-releated Factor 2
ORAC	Oxygen Radical Antioxidant Capacity
PBS	Phosphate Buffered Saline
PD	Parkinson's Disease
PINK1	Phosphatase and Tensin homologue-induced putative kinase 1
ROS	Reactive Oxygen Species
RTE	Ready-to-eat
SEM	Scanning Electronic Microscopy
SN	Substantia Nigra
SOD	Superoxide Dismutase
TFC	Total Flavonoid Content
TPC	Total Phenolic Content
TPTZ	2,3,5-Triphenyltetrazolium chloride
WSI	Water Solubility Index
WHO	Worldwide Health Organization
YFP	Yellow Fluorescence Protein
6-OHDA	6-hydroxydopamine

CHAPTER 1

INTRODUCTION

1.1 Rational and Background

Aging is a complex process that causes physiological integrity and function to deteriorate (Hou et al., 2019), and it is linked to an increased risk of cardiovascular disease, diabetes, neurodegeneration, and cancer. Neurodegenerative diseases are disorders characterized by the progressive degeneration and dysfunction of the nervous system, particularly the neurons in the brain (Brown et al., 2005). These diseases primarily affect the structure and function of nerve cells, leading to their gradual and irreversible loss over time (Lamptey et al., 2022). Neurodegenerative diseases can result in a wide range of symptoms, including cognitive decline, movement problems, and changes in behavior or personality (Dugger & Dickson, 2017). Neurodegenerative disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), and Amyotrophic lateral sclerosis (ALS), have a substantial global health impact (Azam et al., 2021).

Parkinson's disease (PD) is the second most common neurodegenerative disease, and is characterized by progressive worsening of motor symptoms over time (Ou et al., 2021; Poewe et al., 2017). PD is one of the leading causes of disability worldwide (Feigin et al., 2017), and its incidence and disability among neurodegenerative diseases have increased rapidly in recent years (Ou et al., 2021; WHO, 2023). Dyskinesia and painful muscle contractions can cause speech and mobility problems, which are symptoms that lead to high rates of disability and require therapy. Many individuals with PD also develop dementia during their disease (WHO, 2023). Both motor and non-motor problems cause individuals who have PD to become more disabled and have a lower quality of life. As the disease worsens, the condition’s cost rises, putting a financial strain on society, healthcare systems, and patients (Findley, 2007; Huse et al., 2005). People’s health-related quality brought on by PD, and the health system suffers heavy cost for care, rehabilitation, and medication

(Dowding et al., 2006). In 2017, the monetary burden of PD was $51.9 billion, and by 2037, it is projected to have increased to over $79 billion (Yang et al., 2020).

Even though only a few researches have been completed in Thailand, it has revealed that the prevalence of dementia and PD range from 1.8-18% in the age group 50-70 years and it was found to increase up to 30% at the age of 90 years and over (Dharmasaroja et al., 2017; Dharmasaroja et al., 2021; Doungkaew & Taneepanichskul, 2014; Jitapunkul et al., 2009; Vinkers et al., 2004). PD has received recognition as a significant neurodegenerative disease because of its high prevalence, impact on quality of life, and associated economic and social burdens. PD has been identified as a major health burden in nations with developing economies, particularly in low- and middle-income countries (LIMCs) (Bhidayasiri et al., 2023; Prince et al., 2013), because of the difficulties in providing patients with the highest quality of treatment, including a lack of resource, unequal access to effective therapies, or a lack of qualified staff (WHO, 2023).

As a result, preventative interventions, early diagnosis, and appropriate treatment are critically important in reducing the healthcare burden associated with these disorders. PD has no known cure. Most current therapies are symptomatic, using medication to modify neurotransmitters, surgery, and rehabilitation reduce symptoms (WHO, 2023). However, various medicinal plants have been reported to help people manage their symptoms and avoid becoming disabled (Morgan & Grundman, 2017). Medicinal plants have demonstrated neuroprotective effects against PD in previous studies. It may improve antioxidants (Casetta et al., 2005; Darvesh et al., 2010; Prasad et al., 1999; Shukla et al., 2023), decrease neuroinflammation, and inhibit dopamine-metabolizing enzymes and oxidant reduction indicators (Javed et al., 2019; Khazdair et al., 2020). Therefore, this present work aimed to (i) examine the antioxidant capacities of local cultivable plant-based antioxidants described in the list of Thai Food and Drug Administration (FDA) approved dietary supplements obtained from medicinal plants (Food and Drug Administration, 2017), (ii) develop microcapsules containing a standardized extract of *Curcuma longa* L., the promising functional ingredient selected from the mentioned list, and (iii) explore the neuroprotective mechanisms of turmeric extract microencapsules against 6-hydroxydopamine (6-OHDA)-induced neurodegeneration in dopaminergic (DA) neurons using a well-described invertebrate

animal model, *Caenorhabditis elegans* (*C. elegans*). The feasibility of using the obtained microcapsules as a functional ingredient in the food industry has been tested using extruded ready-to-eat (RTE) snacks as a food model.

1.2 Objectives

1.2.1 Conduct a systematic review to evaluate the antioxidant and neuroprotective activities of locally grown plants listed in the Thai FDA-approved dietary supplements.

1.2.2 Evaluate the antioxidant activity of selected standardized extracts and develop microcapsules containing *Curcuma longa* extracts, a promising functional ingredient from the approved list.

1.2.3 Investigate the toxicity and neuroprotective mechanisms of *Curcuma longa* extract microcapsules against 6-OHDA-induced neurodegeneration in dopaminergic neurons using *C. elegans* as a model.

1.2.4 Assess the feasibility of incorporating these microcapsules as functional ingredients in the food industry through their application in extruded snacks.

1.3 Expected Outcomes

1.3.1 Identify medicinal plants with antioxidant activity by conducting a systematic review of plant-based ingredients authorized for use in nutritional supplements.

1.3.2 The effects of medicinal plants' antioxidant activity *in vitro* levels.

1.3.3 The effects of medicinal plants toxicity and neuroprotective effects *in vivo* levels.

1.3.4 Develop microcapsule-based functional food with neuroprotective properties.

1.4 Conceptual Framework

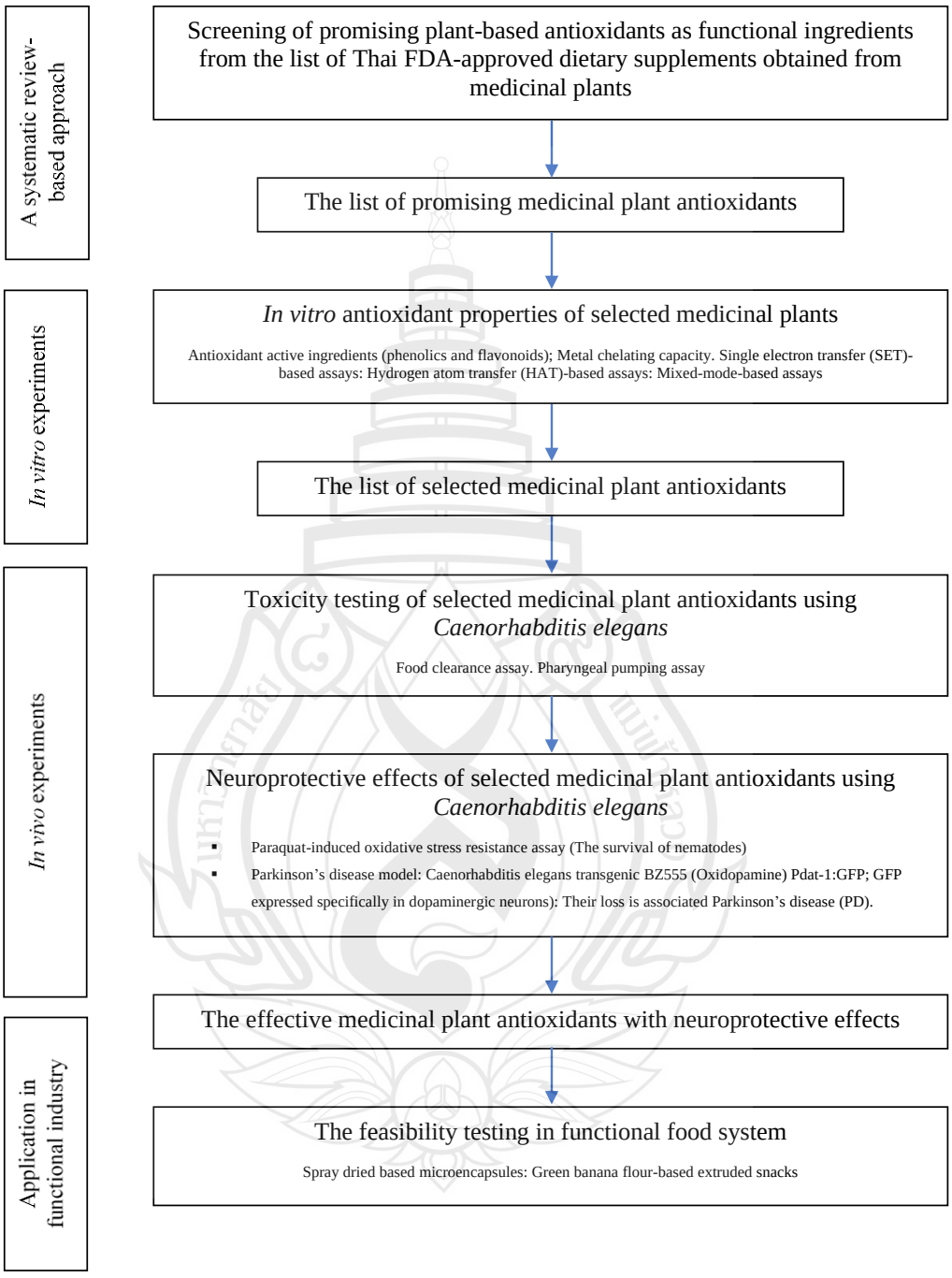


Figure 1.1 Conceptual Framework

CHAPTER 2

LITERATURE REVIEW

2.1 Burden of Neurodegenerative Diseases

2.1.1 Brief Pathophysiology of Parkinson's Disease

Parkinson's disease (PD) affects millions of people worldwide, with symptoms including tremors, stiffness, and difficulty with movement (Muangpaisan et al., 2011). PD can also have a significant impact on an individual's quality of life, as well as their ability to perform daily activities and maintain social relationships. The economic burden of PD is also significant, with estimates suggesting that the cost of care for individuals with PD is billions of dollars each year (von Känel et al., 2011). PD has an unidentified cause. The identification of genetic risk factors in recent years has contributed to the assumption that these factors may be involved in as many as 5-10% of situations (Tysnes & Storstein, 2017). Mutations in the LRRK2 enzyme have been demonstrated in previous studies to account for as much as 40% of all cases of the disease (Lesage & Brice, 2012). Environmental factors are known to have the potential to contribute to the risk of disease, in addition to genetics. Risk factors include living in a rural area, working in farming, drinking groundwater, prior head injuries, and pesticide exposure. Smoking, drinking coffee, using non-steroidal anti-inflammatory medicines, and drinking alcohol are a few environmental factors are less dangerous (Kalia & Lang, 2015; Tysnes & Storstein, 2017).

Parkinson's disease was first described by James Parkinson in 1817, based on his observations of patients with tremors, stiffness, and difficulty with movement (Goetz, 2011). In the decades that followed, researchers identified the underlying pathology of PD as the loss of dopamine-producing neurons in the brain, particularly in a region called the substantia nigra (SN). This discovery led to the development of medications that could replenish dopamine in the brain and improve symptoms of PD (Capriotti & Terzakis, 2016) (Figure 2.1).

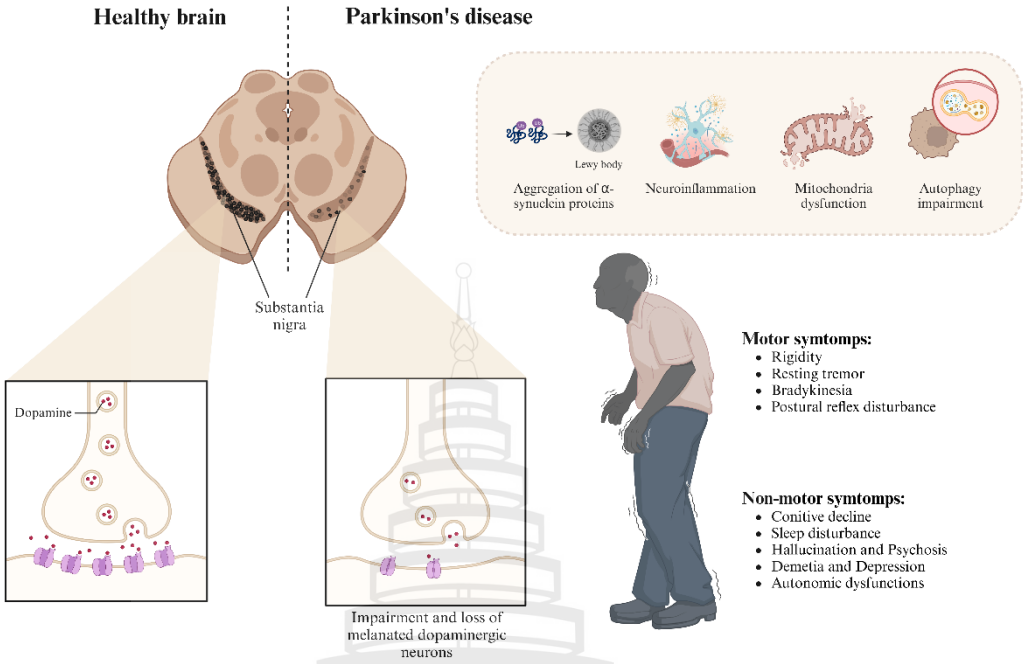


Figure 2.1 Parkinson's disease neuropathological features and the main motor symptoms of the disease, are caused by the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta. Created with BioRender.com.

PD is the second most common neurodegenerative disease in its early stages (Bertram, 2005). PD symptoms include both motor (movement disorder) and non-motor abnormalities (Muangpaisan et al., 2011), hyperkinetic and hypokinetic signs are characteristics of motor movement disorder (Robottom et al., 2011). A disorder characterized by hyperkinetic movement, such as HD (Litvan et al., 1998), which is abnormal involuntary movement including tremors, dystonia, chorea, tics, myoclonus, stereotypies, and restless legs syndrome (Jankovic, 2009). Cardinal symptoms of hypokinetic signs of movement disorder include rigidity, postural instability, bradykinesia, and rest tremors (Capriotti & Terzakis, 2016). Cognitive decline, hallucination and psychosis, sleep disturbances, dementia, depression, and autonomic dysfunction are examples of non-motor symptoms (Park & Stacy, 2009), and quality of life related may be more negatively impacted by non-motor symptoms than motor abnormalities (Weerkamp et al., 2013). PD pathology (Figure 2.1) involves the basal ganglia, especially the SN (Trail et al., 2008). The basal ganglia's role is movement

initiation and voluntary movement control (Blandini et al., 2000). Which is the subsequent loss of dopamine-producing neurons (Dauer & Przedborski, 2003), and the progressive loss of DA neuronal cells in the substantial pars compacta (SNc) (Dexter & Jenner, 2013). PD is characterized by the accumulation of fibrillar aggregates of insoluble α-synuclein, a key protein in the Lewy body (LB) (Sato et al., 2011). Atypical protein synthesis, oxidative stress, and mitochondrial dysfunction are among the pathogenic mechanisms of PD, which contribute to cell death (Pfeiffe et al., 2012).

Parkinson's disease -related genetic mutations include α-synuclein, leucine-rich repeat kinase 2 (LRRK2), Phosphatase and Tensin homologue-induced putative kinase 1 (PINK1), Parkin, and DJ-1 (Table 2.1) (Zeng et al., 2018). The mutation of the SNCA/PARK1 gene encodes protein α-synuclein (Polymeropoulos et al., 1997). LBs and Lewy neurites (LNs) are fibrillary aggregates found in PD, and α-synuclein is a major component of both (Spillantini et al., 1997). Because neural activity dynamically regulates the physiologic release of endogenous α-synuclein, an increase in the release of α-synuclein and an increase in cell-to-cell transmission cause α-synuclein to aggregate (Yamada & Iwatsubo, 2018). In addition, α-synuclein promotes disruption of cellular homeostasis, neurodegenerative, effect on various intracellular targets, and synaptic function. The mutation of α-synuclein is also toxic to DA neurons (Stefanis, 2011). The α-synuclein (A53T) mutations cause endoplasmic reticulum stress-mediated cell death and mitochondrial dysfunction (Smith et al., 2005). LRRK2 is a large protein with several multiple domains (Gandhi et al., 2009). The LRRK2/PARK8 gene encodes the LRRK2 protein (Paisán-Ruíz et al., 2004). Autosomal dominant parkinsonism is frequently caused by a mutation in the LRRK2/PARK8 gene (Zimprich et al., 2004), a pool of α-synuclein with is more prone to producing inclusions is increased by the LRRK2 mutation, which might accelerate the formation of pathogenic α-synuclein (Volpicelli-Daley et al., 2016).

A mitochondrially targeted kinase named PINK1 is a protein that is essential for controlling a variety of mitochondrial pathways (Matsuda et al., 2013), PINK1 is a mitochondrial-targeted serine/threonine kinase that is encoded by the PARK6 gene (Moore et al., 2005). Larger or swollen mitochondria can be found as a result of PINK1 gene mutations (Moon & Paek, 2015). The accumulation of damaged mitochondria induced by the autophagy-lysosome system, which removes damaged mitochondria in

affected neurons, may play a significant role in the pathophysiology of synaptic dysfunction and misfolded protein aggregates (Gao et al., 2017).

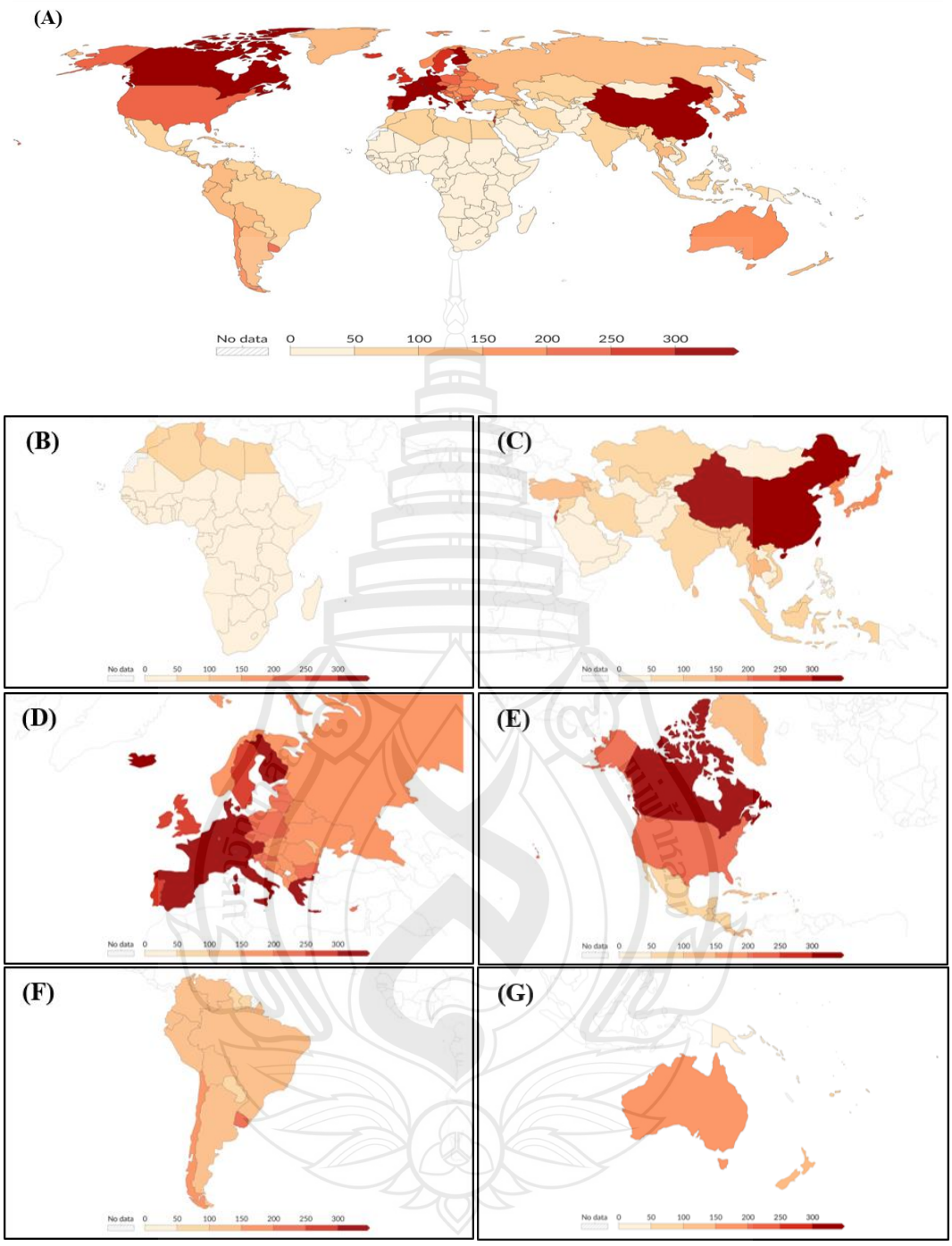
The next genetic mutation Parkin is a ubiquitin E3 ligase, a RING-base, and a member of the protein family with a conserved ubiquitin-like domain (UBL) (Deshaies & Joazeiro, 2009), that regulates several cellular functions by monoubiquitinating and polyubiquitinating protein (Dawson & Dawson, 2010). Because PINK1 functions in a mitochondrion quality-control mechanism mitophagy, which is upstream of Parkin, autophosphorylated PINK1 can activate Parkin (Zhuang et al., 2016). To increase mitophagy of malfunctioning mitochondria after the loss of mitochondrial membrane potential, PINK1 aggregated on the membrane of dysfunctional mitochondria and activated Parkin's E3 ubiquitin ligase activity (Narendra et al., 2009). Due to the increased production of reactive oxygen species (ROS) both within and outside of the mitochondria during the early stages of PD, oxidative stress has been directly related to both its onset and development (Zhou et al., 2008), by encouraging Parkin recruitment to mitochondria, ROS serve as a catalyst for the activation of Parkin and PINK1-dependent mitophagy (Xiao et al., 2017). Parkin and PINK1, which are mutated in autosomal parkinsonism, collaborate on the same pathway to modulate mitochondrial quality (Pickrell & Youle, 2015). The DJ-1 mutation, as encoded by the PARK7 gene (Bonifati et al., 2003), DJ-1 protein functions as a molecular chaperone, enzyme, and oxidative stress sensor, it also controls transcriptional and signal transduction pathway, scavenges free radical ROS, and regulates transcription (Kahle et al., 2009). DJ-1 mutation interacts with α-synucleinopathy and reverses the cellular damage caused by α-synuclein (Taipa et al., 2016).

2.1.2 Prevalence and Health Burden of Parkinson's Disease

Globally, neurodegenerative diseases are an important cause of mortality and disability. Due to increasing populations and aging, the prevalence of neurodegenerative diseases has significantly increased globally during the past 25 years (Karikari et al., 2018). PD, the second most common neurodegenerative disease after Alzheimer's disease, is a progressive neurodegenerative disorder that is most prevalent among adults of middle age and older ages (Bertram, 2005).

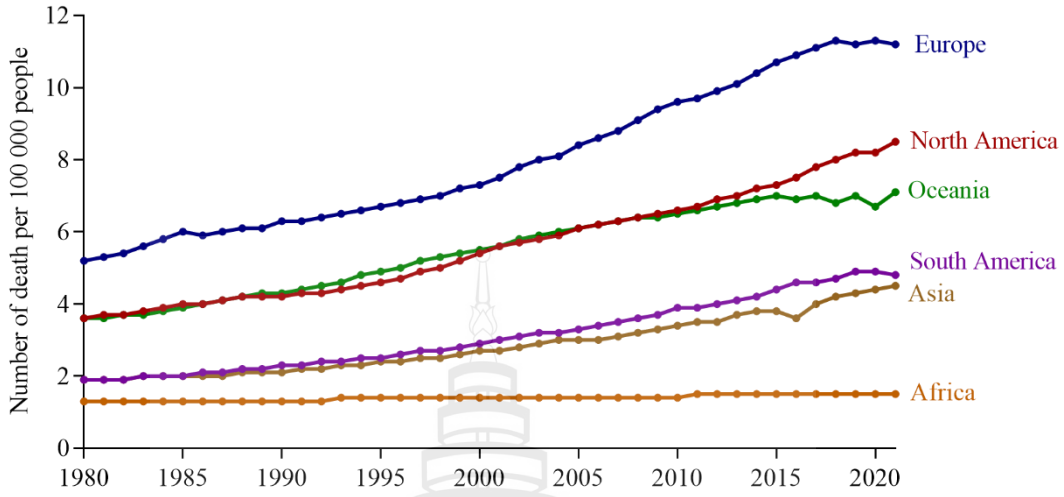
In terms of age-standardized prevalence, disability, and mortality, PD is estimated to be a neurodegenerative disease with the fastest rate of growth in the world (Bhidayasiri et al., 2024; Dorsey et al., 2018). According to World Health Organization (WHO) data from 2021, there are over 11.77 million PD cases globally, which is a considerable rise from the 2.50 million cases recorded in 1990 to the 8.50 million cases reported in 2016 and 6.10 million cases reported in 2019 (Dorsey et al., 2018; GBD 2019 Dementia Collaborators, 2021; Luo et al., 2025; Xu et al., 2023). The estimated global incidence of PD per 100,000 people in 2021 is shown in Figure 2.2. In Europe, there were 246.60 cases of PD for every 100,000 people, compared to 227.80 cases in North America, 162.30 cases in Asia, 124.80 cases in Oceania, 115.60 cases in South America, and 25.60 cases in Africa (IHME, Global Burden of Disease, 2024).

The estimated global number of PD deaths per 100,000 people from 1980 to 2021 (Figure 2.3). Each continent has an increasing annual number of deaths from PD. Between 1980 and 2021, the number of PD-related deaths in Europe rose from 5.20 per 100,000 to 11.20 per 100,000. The corresponding statistics for North America (3.60-8.50 per 100,000), Oceania (3.60-7.10 per 100,000), South America (1.90-4.80 per 100,000), Asia (1.90-4.50 per 100,000), and Africa (1.30-1.50 per 100,000) hold (IHME, Global Burden of Disease, 2024).



Source IHME, Global Burden of Disease (2024)

Figure 2.2 The estimated global number of people with Parkinson's disease per 100,000 people in 2021. (A) Worldwide, (B) Africa (C) Asia, (D) Europe, (E) North America, (F) South America, and (G) Oceania



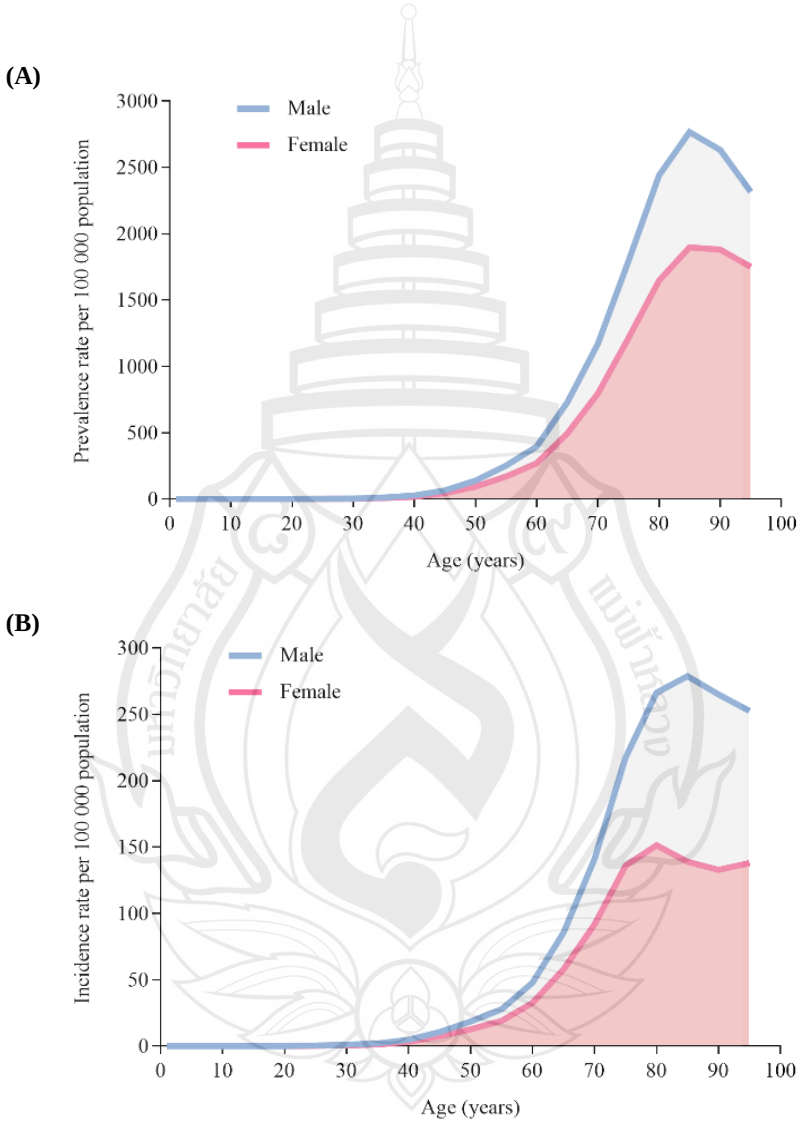
Source IHME, Global Burden of Disease (2024)

Figure 2.3 The estimated number of deaths with Parkinson's disease per 100,000 people in 1980 to 2021

Males are more inclined than females to have PD, and the disease's burden slightly varies with age. Figure 2.4 shows the 2021 incidence and prevalence rates per 100,000 people. Both males and females were found to have significant rates of PD incidence and prevalence in the 70-95 age range. PD prevalence rates were 1,170.42-2,316.08 and 796.05-1,750.04 per 100,000 population, while the incidence rates for males and females were 140.96-252.50 and 91.69-137.88 per 100,000 population, respectively (GBD results, 2021). According to predicts of the global burden of PD for the next 25 years until 2050 (Figure 2.5), the estimated number of deaths, Years Lost due to Disability (YLDs), and Disability-Adjusted Life Years (DALYs) per 100,000 people worldwide increases annually including in Southeast Asia, where the mortality rates for PD are also increasing (GBD Foresight Visualization, 2025).

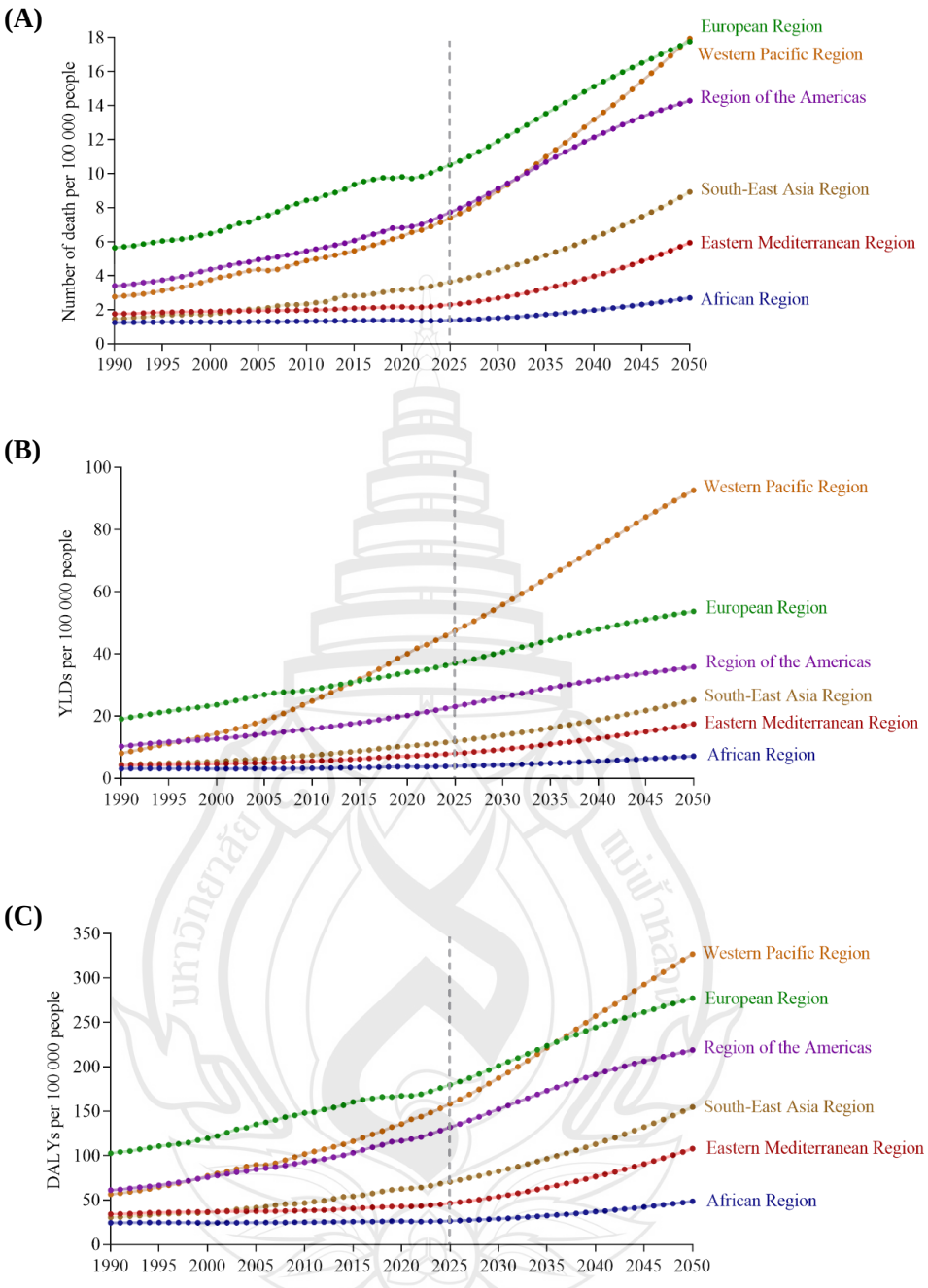
Asia has one of the highest incidences of neurodegenerative disease morbidity and mortality worldwide. The top 5 Asian nations with the highest incidences of PD mortality in 2019 are Japan, Thailand, Turkey, South Korea, and Kazakhstan, respectively, the death rate per 100,000 population and percentage of cause-specific death out of total deaths in Japan 38.04 (3.41%), Kazakhstan 29.81 (4.15%), Thailand 24.83 (3.29%), South Korea 20.36 (3.54%), and Turkey 16.97 (0.79%) (WHO,2022).

Thailand comes in second place for the number of deaths from neurodegenerative disease in Asia. PD ranks as the top 10 leading cause of mortality in Thailand among top 10 diseases with the highest frequency among people 85 years of age and above (WHO, 2022). The DALYs rate for PD was 1,503.09 per 100,000 population, and the death rate was lower at 182.48 deaths per 100,000 (Figure 2.6).



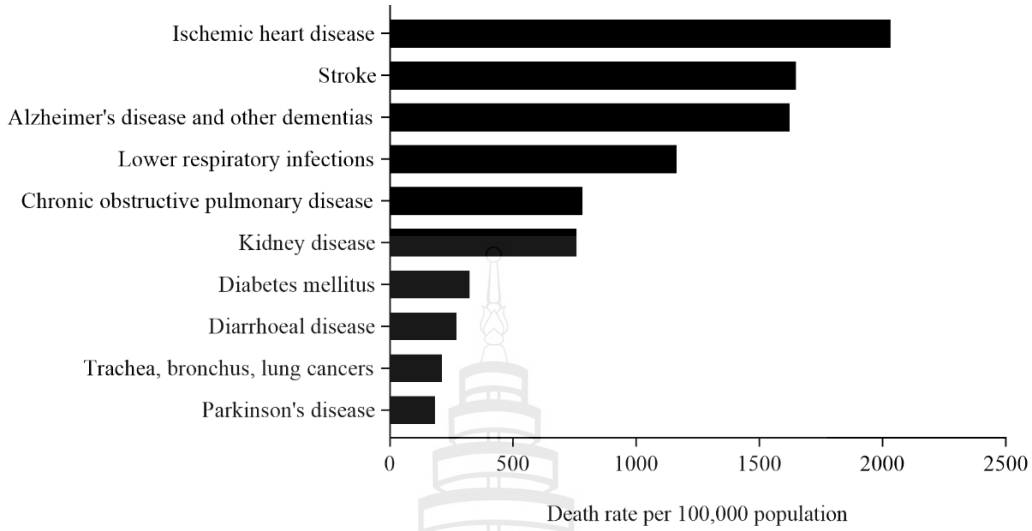
Source The 2021 Global Burden of Disease (GBD) study

Figure 2.4 The global disease burden of Parkinson's disease by age and sex in 2021. (A) Prevalence rate and (B) Incidence rate per 100,000 people



Source Global Burden of Disease (GBD) (2025)

Figure 2.5 The prediction of the global burden associated with Parkinson's disease, in 2050, (A) Causes of death, (B) YLDs, and (C) DALYs per 100,000 people



Source World Health Organization (WHO): Global health estimates: Leading causes of DALYs, 2019. DALYs, the disability-adjusted life year

Figure 2.6 The leading causes of death in Thai elderly aged

2.1.3 Caregiver Burden Associated with Parkinson's Disease

As the elderly population has dramatically increased neurological disorder particularly PD becomes a more common symptom. Because there is no cure for PD or a strategy to slow their progression, one of the major golds should be to enhance and sustain the psychological, physical, employment, and financial outcomes of balancing multiple caregiving duties, especially in the sandwich generation. Caregiving for a person who has neurodegenerative diseases including PD is frequently very difficult. The loss of patient autonomy in PD may have an impact on function and decrease quality of life (QoL) (Modugno et al., 2020) and health-related life quality of life (HRQoL) in caregivers (Martínez-Martín et al., 2007). As a result, caregivers frequently experience high emotional stress and depression, which also negatively affects their health, employment, income, and financial security.

People with PD may suffer from cognitive impairment because of pathology or treatment-related side effects, which are major determinants of patient QoL and caregiver burden (Rektorova, 2019), over 40% of caregivers reported that their suffered as a result of their caregiving (Schrag et al., 2006), which the main factors impacting caregiver burden in PD are patients' and corer's depression and anxiety mood (Torny

et al., 2018), and 2 out of 3 reported that their social lives suffered (Schrag et al., 2006). Report to Santos-García and De la Fuente-Fernández (2014) the main causes of burden and stress in caregivers are disability, as evaluated by the Activities of Daily Living Scale (ADLS), and mood, as determined by the beck depression inventory (BDI) of patients with PD, Zarit Caregiver Burden Inventory and caregiver strain index (CSI) both assess levels of stress in caregivers. Caregiver stress and depression are significantly impacted by non-motor symptoms of diseases more than 0-6% of the patient's motor symptoms are 7-13% (Carter et al., 2008), and caregiver burden increased as disability and PD symptoms worsened (Martinez-Martin et al., 2012; Schrag et al., 2006) patients who experience neuropsychiatric symptoms report a high level of distress (Oh et al., 2015), especially when it came to issues with mental health including symptoms of apathy, depression, anxiety, hallucination, confusion, and irritability (Leiknes et al., 2010; Oh et al., 2015; Schrag et al., 2006), caused caregiver distress more frequently in 50% of PD patients than in non-caregivers (Leiknes et al., 2010).

The general health of caregiver's people with PD encountered problems daily 30% with weariness and sleep disturbances, 27% with hypertension, 17% with muscle soreness, headaches, and lethargy, and 14% with gastrointestinal conditions (Lökk, 2008). In addition, Happe and Berger (2002), found that sleep disturbances and depression symptoms are common in caregivers with PD and 27% of spouses who are also caregivers experience frequent sleep problems.

Data from the NAC and the AARP Public Policy Institute (2020), 6 in 10 caregivers report that their employment situations have changed as a result of providing care, and many high-hour caregivers are more impacted by caregiving than low-hour caregivers, as seen by the fact that 27% high-hour caregivers lowered working hours, 26% took a leave of absence, 13% declined a promotion, 13% quit employment entirely, and 10% retired early (AARP & National Alliance for Caregiving, 2020).

The economic burden of PD caregivers, who are primarily family members, impacts both the patient and their direct family (Martinez-Martin et al., 2012), in Eastern European nations, the cost of PD in both patient long-term care and medicine ranges from €2,626 to €9,820 (von Campenhausen et al., 2011), which antiparkinsonian drug, which is quite expensive is the main financial burden on PD patients. The overall

cost for 6 months was €8,640, with health insurance making up 39.6% of the cost (Winter et al., 2010).

2.2 Neurodegenerative Potential of *Curcuma longa*: Mechanistic Insights and Limitations

Curcuma longa, commonly known as turmeric, has been the subject of numerous studies exploring its potential as a treatment for various diseases, including cancer, cardiovascular disease, obesity, liver disease, inflammatory disease, aging, and neurodegenerative diseases (Monroy et al., 2013). This study delves into its traditional use, solubility, stability, pharmacokinetics, bioavailability, mechanism of action, and limitations to understand its effectiveness in treating these conditions, with a particular focus on neurodegenerative diseases.

2.2.1 *Curcuma longa*: Traditional use, Solubility, and Stability

Curcuma longa is a member of the ginger family (Zingiberaceae) and has rhizomes that are multi-branched (The World Flora Online, 2022). Turmeric has many names such as Curcum in the Arab region, Indian saffron, Haridra (Sanskrit, Ayurvedic), Jianghuang (yellow ginger in Chinese), and Kyoo Ukon (Japanese) (Goel et al., 2008), commonly used in India, turmeric is a golden spice that also uses as a textile color and for food preservation (Aggarwal et al., 2007) has been in Asia cuisine for its flavor and color as well as in Chinese, Japanese, Korean, and Ayurvedic medicine for a variety of conditions, including colic, jaundice, menstruation problems, hematuria, and bleeding (Labban, 2014).

Turmeric is a medication used in Ayurveda and traditional Chinese medicine to treat various diseases, it is used as an anti-inflammatory to treat conditions like colic, gas, toothaches, chest pains, menstrual difficulties, stomach and liver problems, as well as for cosmetic purposes (Aggarwal et al., 2007). A compound of curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (Bis-DMC) has an inhibitory effect on OVCAR-3 cells from human ovarian cancer (Syu et al., 1998), and an antitumor effect in a panel of human tumor cell lines (Abas et al., 2005). *In vivo*, curcuminoids can lower lipid levels, liver triacylglycerol, and cholesterol

concentrations were also decreased (Asai & Miyazawa, 2001) and there were decreased levels of total plasma cholesterol, phospholipids, and triglycerides in individuals who consumed curcumin extracts, which have pharmacological effects on plasma and low-density lipoprotein (LDL) lipid composition (Ramírez-Tortosa et al., 1999), in the study of Akhilender and Thippeswamy (2002) curcumin successfully prevented both the start and propagation phases of LDL oxidation in human and had the highest antioxidant activity of about 1-4%. In study *in vivo* model found when rats were given cholesterol and no curcumin, the level of serum and liver cholesterol decreased one-half or one-third of those levels (Rao et al., 1970), exhibiting-inflammatory activity after parenteral administration (Ammon & Wahl, 1991), and curcumin decreased inflammatory disease by preventing experimental allergic encephalomyelitis (EAE) and lowering T-cell IL-12 production signaling (Natarajan & Bright, 2002). In addition, curcumin causes the epidermis to re-epithelize, and it also causes more fibroblasts, macrophages, and myofibroblasts to migrate and deposit greater collagen in the wound bed (Sidhu et al., 1998). Turmeric was inferior to curcumin in attenuating the effects of diabetes mellitus on blood sugar, hemoglobin, and glycosylated hemoglobin levels in diabetic rats (Arun & Nalini, 2002). For patients with quiescent ulcerative colitis (UC) who want to keep their remission, curcumin is a promising and safe therapy (Hanai et al., 2006).

The conclusions of a joint Food and Agriculture Organization of the United Nations (FAO) and WHO evaluate the safety of various food additives in 2004, stated the acceptable daily intake of curcumin as a food additive in the range of 0-3 mg/kg of body weight, up to 1.5 g of turmeric/person/day, or a maximum of 150 mg of curcumin/day (Sharma et al., 2005) and 2.2 g/day, or 180 mg (Sharma et al., 2001), is safe to consume dietary without experiencing negative effects in people. Even at high doses of 12 g/day, curcumin is safe, however, it has poor bioavailability (Anand et al., 2007).

Worldwide Health Organization (WHO): monographs on selected medicinal plants describe the turmeric's organoleptic properties, orange or bright yellow, and aromatic flavor that is also bitter when drugs are chewed the saliva turns yellow, and the purity test of turmeric, foreign organic matter not more than 2%, total ash not more than 8%, acid-insoluble ash not more than 1%, water-soluble extractive not less than 9%, alcohol-soluble extractive not less than 10%, the moisture not more than 10%,

pesticide residues maximum residue limit of aldrin and dieldrin in the rhizome is not more than 0.05% mg/kg, and heavy metals lead level not more than 10 mg/kg and cadmium level not more than 0.3 mg/kg (WHO,1999).

Curcumin, the main bioactive compound of *Curcuma longa* is a polyphenol, chemical name [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-33,5-dione] (Lestari & Indrayanto, 2014), the chemical of turmeric constituents are as follows; curcuminoids make up 1-6% of turmeric's major phytocomponents, volatile (essential) oils 3-7%, fiber 2-7%, mineral matter 6-8%, fat 5-10%, protein 6-12%, carbohydrates 60-70%, and moisture 13.1%, protein (Eigner & Scholz, 1999; Nelson et al., 2017). The essential oil (5-8%), obtainable by steam distillation of the rhizomes, has the α-phellandrene 1%, sabinene 0.6%, cineol 1%, borneol 0.5%, zingiberene 25%, and sesquiterpenes 53% (Eigner & Scholz, 1999), which combine to form a pale yellow to orange-yellow volatile oil (WHO,1999). Turmeric contains phytochemicals including curcumin, DMC, Bis-DMC, zingiberene, curcumenol, curcumol, eugenol, tetrahydrocurcumin, triethylcurcumin, turmerin, turmerones, and turmeronols (Aggarwal et al., 2007). The molecular formula of curcumin is $C_{21}H_{20}O_6$ (Figure 2.6) and has a molecular weight of 368.38 Daltons (Royal Society of Chemistry, 2022), there are 3 different curcumin analogs found in turmeric, diferuloylmethane (also known as curcumin), DMC, and Bis-DMC (Aggarwal et al., 2007). 1-6% of curcuminoids by weight, distributed as 60-70% curcumin, 20-27% DMC, and 10-15% Bis-DMC (Aggarwal et al., 2007; Nelson et al., 2017; WHO,1999). Curcumin, DMC, and Bis-DMC have also been isolated from *Curcuma manga* (Abas et al., 2005), *Curcuma zedoaria* (Syu et al., 1998), *Curcuma phaeocaulis*, *Curcuma aromatica* (Tohda et al., 2006), and *Etlingera elatior* (Mohamad et al., 2005). In addition, DMC and Bis-DMC, 2 naturally occurring derivatives of curcumin, have different structures and activities, which discovered curcumin to be the most efficient (Ahsan et al., 1999), curcumin accounts for around 90% of the curcuminoid content in *Curcuma longa* (Labban, 2014).

The solubility of curcumin was not solved with water as a solvent at normal temperature (Wang et al., 2009), in water with an acidic or neutral pH, curcumin is essentially insoluble (hydrophobic), but it is soluble in polar and nonpolar organic solvents such as dimethylsulfoxide, acetone, ethanol, acetic acid, and oils (Aggarwal et

al., 2007; Sharma et al., 2005), in general, the stability of curcumin is pH>1, curcumin solution is red in color due to the presence of the protonated form, pH 1-7, curcumin solution is yellow with the majority of the molecules being in the neutral form, pH>7.5, curcumin solution color change to orange-red (Lestari & Indrayanto, 2014) and at pH 2.5-7.0, it is brilliantly yellow in color, and at pH 7.0 or above it turns red (Aggrawal et al., 2003).

The kinetics of curcumin's degradation occurred rapidly in buffer solution at 37°C and neutral to basic pH level, within 30 minutes, vanillin, ferulic acid, and trans-6-(40-hydroxy-30-methoxyphenyl)-2,4-dioxo-5-hexanal were produced (Wang et al., 1997) because the melting point of curcumin is 183°C (Royal Society of Chemistry, 2022) when heated for 10 minutes, curcumin was stable up to 70°C, but once this point is higher curcumin starts to degrade more rapidly, and at 100°C, this degradation accelerates (Wang et al., 2009), and curcumin loss from heat processing to turmeric was 27% and 32% when it was boiling for 10 or 20 minutes, whereas 53% less curcumin was lost when it was put through a pressure cooker for 10 minutes (Suresh et al., 2007).

In addition, curcumin is a cyclization product of curcumin formed by the loss of two hydrogen atoms from the curcumin molecule, when subjected to UV/Visible radiation, curcumin can photodecompose both in solution and in a solid state (Tønnesen et al., 1986), and further studies have found that curcumin is a potential photosensitizing drug, by irradiation with visible light, proves to be phototoxic for the bacterial test systems used (Tønnesen et al., 1987), which curcumin absorbs most strongly at 415-420 nm in acetone according to spectrophotometry, and a 1% solution of pure curcumin has an optical density of 1650 absorbance units (Aggarwal et al., 2003) and curcumin fluorescence is a broad band in acetonitrile (λ_{max}=524 nm), ethanol (λ_{max}=549 nm), and micellar solution (λ_{max}=557 nm), which in acetonitrile (max=524 nm), ethanol (max=549 nm), and micellar solution (max=557 nm), curcumin fluorescence's over a wide wavelength range (Chignell et al., 1994), by preventing deterioration from light, which is brown glass can be used to store or protect curcumin from light because this form of glass only transmits light with wavelengths above 500 nm, for which curcumin has no absorption (Tønnesen et al., 1986). However, curcumin's phenolic group enables it to neutralize oxygen-derived free radicals, and curcumin is a potent inhibitor of lipid peroxidation brought on by r-radiation (Goel et al., 2008).

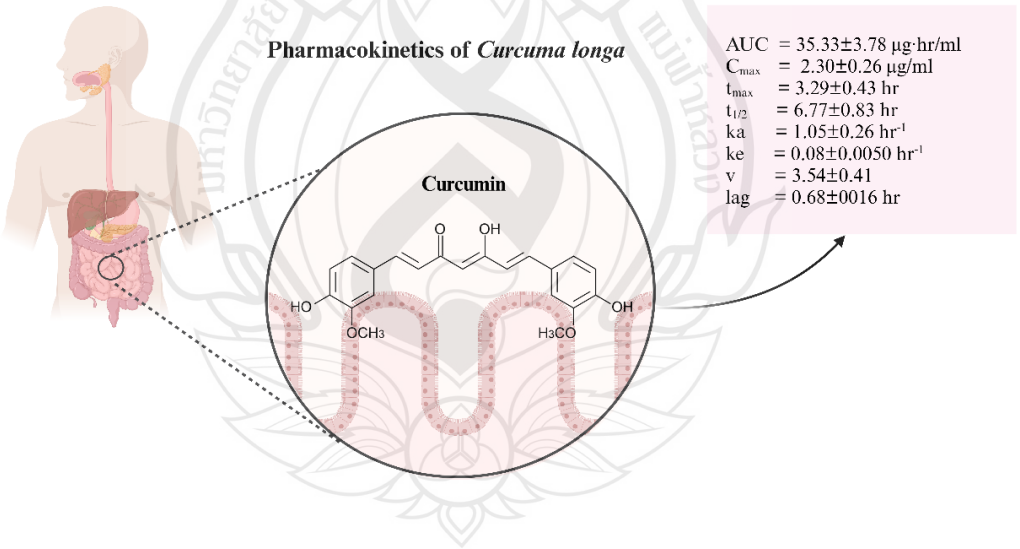
2.2.2 Pharmacokinetic and Bioavailability of Curcumin

In humans, curcumin has low oral bioavailability in the gastrointestinal tract and is metabolized in the intestine, and most of it is excreted in the feces (Ammon & Wahl, 1991; Ravindranath & Chandrasekhara, 1980; Sharma et al., 2001), following oral administration, over 60% of the curcumin was absorbed, over the period of 5 days, nearly 40% of the curcumin was eliminated intact in the stool (Ravindranath & Chandrasekhara, 1980). Curcumin has poor oral bioavailability due to poor solubility, rapid metabolization, a poor pharmacokinetic profile, and elimination, curcumin has limited bioavailability, it has limited efficacy when delivered in standard oral forms and consequently low plasma and tissue levels (Anand et al., 2007; Kurita & Makino, 2013). Curcumin plasma concentrations were used to estimate the area under the curve (AUC) value for the pharmacokinetic analysis (Marczylo et al., 2006), AUC reflects the actual body exposure to the drug after the administration of a dose of the drug (Figure 2.7), shown as curcumin administered at a dose of 10 g, and the pharmacokinetics of the drug was studied in healthy human volunteers up to 72 hours after a single oral administration, result showed that the drug had an AUC 35.33±3.78 μg·hour/mL, C_{max} 2.30±0.26 μg/mL, t_{max} 3.29±0.43 hours, $t_{1/2}$ 6.77±0.83 hours, ka 1.05±0.26 $hour^{-1}$, ke 0.08±0.0050 $hour^{-1}$, v 3.54±0.41, and lag 0.68±0016 hour (Vareed et al., 2008).

The biopharmaceutics classification system (BCS) classified curcumin as a class IV molecule, the study evaluated the permeability of curcumin in Caco-2 cell monolayers, curcumin was found to be poorly permeable across the Caco-2 cell monolayers. The major barriers to its passage are cellular accumulation, metabolism, and degradation in Hank's salt solution (HBSS) buffer; after 2 hours, 52% of curcumin has accumulated in the remaining cells (Wahlang et al., 2011). The enhanced bioavailability of curcumin when administered as a complex with phospholipids increases the plasma AUC 0-120 minutes for curcumin after administration of Meriva, plasma, intestine mucosa, and liver specimens exhibited the patient's curcumin peak plasma concentration and AUC values that were 5 times higher than those seen after taking unformulated curcumin (Marczylo et al., 2006). In a study that examined the effect of a curcumin self-emulsifying drug delivery system (SEDDS) on the pharmacokinetics of oral docetaxel administered to rats, AUC and C_{max} values of docetaxel were significantly increased. In the treatment time intervals of 1, 15, and 30

minutes, the AUC values increased to 2 times 539.8±126.1, 1004.1±183.4, and 1099±173.6 mg hours/mL and 2.2, 4.7, and 4.6 times greater than the comparable value in the control group and C_{max} value, respectively (Yan et al., 2011), which promising delivery methods for curcumin orally include solubilization agents that lipid-based formulations play an important role in the permeation of solubilized curcumin (Yu & Huang, 2011).

Therefore, some poorly water-soluble, highly lipophilic drugs can have their oral bioavailability increased by using formulations with natural or synthetic lipids (Porter et al., 2007), a variety of factors such as food processing (grinding, drying, and heating), origin (climate, soil, plant stresses, and storage), and macronutrients might impact the bioavailability of polyphenols in dietary sources (especially dietary lipids) may affect curcumin solubility and absorption (Dei Cas & Ghidoni, 2019) and increase the daily intake of curcuminoids, turmeric should be included in dishes that include lecithin-rich ingredients like eggs or vegetable oil (Cuomo et al., 2011).



Source Vareed et al. (2008)

Figure 2.7 Chemical structures and bioavailability of chemical constituents obtained from *Curcuma longa*. Pharmacokinetic parameters derived from PK model curcumin: Area Under the Curve (AUC); peak concentration (C_{max}); time of peak concentration (t_{max}); half-life ($t_{1/2}$); absorption constant (ka); excretion constant (ke); bioavailability/volume (v); absorption lag (lag). Created with BioRender.com.

2.2.3 *In vitro* Neuroprotective Effects of *Curcuma longa*

In the study conducted by Pandey et al. (2008), the catecholaminergic SH-SY5Y cell line was employed to investigate the impact of curcumin on α-synuclein protein aggregation. The study revealed that the introduction of curcumin led to the inhibition of aggregation in a dose-dependent manner. This effect was accompanied by an increase in the solubility of α-synuclein and a notable reduction of over 32% in the aggregation of mutant α-synuclein within 48 hours. These findings suggest that curcumin possesses the ability to impede the aggregation of the α-synuclein protein, which could potentially have implications for the development of treatments targeting protein aggregation-related disorders such as PD (Table 2.1).

The protective effect of curcumin was attributed to several mechanisms. It effectively the cytotoxicity impact of aggregated α-synuclein, resulting in a decrease in intracellular ROS levels. Curcumin also played a role in preventing apoptosis by inhibiting caspase-3 activation and mitigating signs of apoptotic activity (Chen et al., 2006; Liu et al., 2011; Wang et al., 2010). Furthermore, the study revealed that both intracellular ROS and extracellular oligomeric α-synuclein contributed to cytotoxic effects on the cell culture, inducing caspase-3 activation and triggering apoptosis. This implies that curcumin's ability to counteract these cytotoxic processes could be valuable in protecting cells from the damaging effects of aggregated α-synuclein.

Curcumin treatment led to a notable reduction in behavioral impairment caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in both cell-based and *in vivo* models. Moreover, the therapy increased the survival of tyrosine hydroxylase-positive neurons in the SN, a critical area affected by PD. Additionally, curcumin exhibited a substantial reduction in the phosphorylation of JNK (c-Jun N-terminal kinase) and the cleavage of caspase-3, both of which are implicated in cell death pathways (Yu et al., 2010). In a study conducted by Du et al. (2012) the cytoprotective effects of curcumin against 6-OHDA-induced neuronal death were investigated in MES23.5 cells. The study aimed to uncover the underlying mechanisms of curcumin's neuroprotection. The findings revealed that curcumin demonstrated the ability to safeguard MES23.5 cells from neurotoxicity induced by 6-OHDA. This protective effect was achieved through several mechanisms. Curcumin partially restored the mitochondrial membrane potential, raised the levels of Cu-Zn superoxide dismutase (an

antioxidant enzyme), and reduced the increase in intracellular ROS. Additionally, curcumin inhibited the translocation of nuclear factor-kappaB (NF-kB) induced by 6-OHDA. These results highlight curcumin's potential to exert neuroprotective effects against 6-OHDA-induced neuronal death. The study suggests that curcumin could be considered a low-toxicity treatment for PD, given its ability to counteract the damaging effects of neurotoxicity and oxidative stress associated with the condition. This insight offers promise for the development of novel strategies for managing PD using natural substances like curcumin.

2.2.4 *In vivo* Neuroprotective Effects of *Curcuma longa*

2.2.4.1 Non-vertebrate models

Caenorhabditis elegans (C. elegans) and *Drosophila melanogaster* (*D. melanogaster*) are widely utilized invertebrate models for studying Parkinson's diseases, as shown in Table 2.1. These models are advantageous due to their amenability to genetic modification for the creation of transgenic models. They are particularly suitable for large-scale screenings of abnormal genes. In the study conducted by Liao et al. (2011), the effects of curcumin on lifespan and aging were explored using the model organism *C. elegans*. The findings revealed several significant outcomes. Curcumin administration was associated with an increase in the lifespan of *C. elegans*, suggesting a potential role for curcumin in promoting longevity. Concurrently, curcumin treatment led to a decrease in intracellular ROS and lipofuscin accumulation, both of which are associated with the aging process. The study also identified specific effects of lifespan extension. While curcumin treatment extended lifespan, it was found to impact body size and the rate of pharyngeal pumping, which is a feeding behavior, without influencing reproduction. Furthermore, curcumin therapy demonstrated the ability to increase the lifespan of *C. elegans* mutants, suggesting a potential role for curcumin in counteracting factors that impact lifespan.

A study by de Guzman et al. (2022) focused on investigating the effects of curcumin-loaded human serum albumin (HAS) nanoparticles on symptoms resembling PD in *C. elegans*, a model organism commonly used in research. The results found that administering curcumin-loaded HAS nanoparticles orally had positive effects on PD-like symptoms in the worms. These symptoms included improved body movement, basal slowing response, and protection against the degeneration of dopaminergic

neurons. Furthermore, the study revealed that the nanometer-size particles containing curcumin and encapsulated within HAS (referred to as CUHNP) had a beneficial impact on the lifespan of *C. elegans*. The worms that received CUHNP supplementation exhibited a longer lifespan of approximately 2-3 days, which correlated with the observed enhancement in their movement abilities. These nanoparticles might act as dopamine transporters, contributing to the safeguarding of dopamine neurons. This protection of dopamine neurons appeared to prevent the development of symptoms resembling those seen in PD. Overall, the study suggested that curcumin-loaded HAS nanoparticles, particularly in the form of CUHNP, could hold promise for potential therapeutic application in managing PD-related symptoms and promoting neuronal health.

Curcumin treatment was investigated in the *D. melanogaster* model of PD, the study revealed several positive effects of curcumin. Administration of curcumin resulted in improved movement in the affected *D. melanogaster*, indicating a beneficial impact on their impaired locomotion (Lee et al., 2010; Nguyen et al., 2018). Additionally, curcumin treatment showed promise in reducing neurotoxicity, suggesting a potential protective effect against neuron damage. Notably, curcumin had a significant influence on ROS levels in flies with suppressed dUCH gene expression, a hallmark of the PD model. The heightened ROS levels due to dUCH reduction were notably lowered after curcumin administration (Nguyen et al., 2018). This discovery suggested that curcumin might possess antioxidant properties capable of counteracting the oxidative stress associated with the PD model. Additionally, Phom et al. (2014) investigated the protective effects of curcumin, a genotropic drug with neuroprotective properties in PD, using a *D. melanogaster* model. The study demonstrated that curcumin's ability to restore dopamine levels was only effective during the early stages of the PD model's life cycle, highlighting the limitations of gonotrophic drugs for conditions like PD that have a late onset of neurodegenerative disease.

2.2.4.2 Vertebrate models

Numerous *in vivo* tests confirmed that curcumin can offer neuroprotection in the context of PD by protecting tyrosine hydroxylase (TH)-positive cells in the SN, a region that is crucial to the production of dopamine. After the administration of curcumin daily for 7, 10, and 90 days the rats, dopamine levels in the striatum were

significantly lower (Mansouri et al., 2012; Mythri et al., 2011; Tripanichkul & Jaroensuppaperch, 2012; Zbarsky et al., 2005). The study concluded that regular consumption of curcumin-containing foods could safeguard the brain against the neurotoxic consequences associated with PD, highlighting the potential neuroprotective effects of curcumin in this context. This is consistent with the study of Rajeswari (2006) the aim was to investigate whether curcumin offers neuroprotection in a rat model of PD induced by 6-OHDA. The study assessed various parameters related to oxidative stress and antioxidant defenses in the SN and midbrain, measured reduced glutathione, a key antioxidant; LPO levels indicated by thiobarbituric acid reactive substances (TBARS); and the activity of antioxidant enzymes catalase (CAT) and superoxide dismutase (SOD). The findings revealed that curcumin administration had positive effects on antioxidant enzyme activities (SOD and CAT) in the presence of 6-OHDA. Even after curcumin administration was stopped, its effects on these enzymes persisted. The study demonstrated that curcumin could counteract LPO and depletion of reduced glutathione induced by 6-OHDA in both the striatum and midbrain regions. In conclusion, the study provides solid evidence that curcumin plays a role in protecting neurons from oxidative stress in a rat model of PD induced by 6-OHDA. The observed effects on antioxidant enzyme activities and oxidative stress markers suggest curcumin's potential as a neuroprotective agent in PD.

2.2.5 Clinical Studies Neuroprotective Effects of *Curcuma longa*

There are various restrictions on human Parkinson's disease research, this is due to research that uses tissue from patients who have passed away to find faulty genes in humans. The majority of these are in the last stages of the disease and may be picky about the ethics and methodology of human research. Consequently, the majority of clinical studies have only been on aged, healthy individuals as shown a Table 2.1.

In the study by Ghodsi et al. (2022) evaluated the effectiveness of adding nanomicelle curcumin 80 mg/day in idiopathic PD patients aged 30 in a test pilot, randomized, triple-blind, placebo-controlled, add-on experiment that was followed for 9 months. The results showed that there was no significant difference in the Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Parkinson's Disease Questionnaire (PDQ-39) score between the curcumin and placebo groups at any time points, and side effects of curcumin included

nausea, vomiting, and gastroesophageal reflex. While examined the effects of curcumin supplementation on clinical scales and misfolded, phosphorylated α-synuclein accumulation in PD patients. The effects of curcumin supplementation over a 12-month period were evaluated using specific questionnaire to objectively define autonomic (COMPASS-31), motor (MDS-UPDRS-III in off state and Hoehn and Yahr scale [H&Y] score) and nonmotor (Non-Motor Symptoms Scale [NMSS]), and skin biopsies to assess clinical involvement. The results showed that curcumin treatment significantly reduced the worsening of the clinical parameters and skin α-synuclein accumulation compared to patients who were not treated, in addition, to a decrease in COMPASS-31 and NMSS score (Donadio et al., 2022).

Table 2.1 Neuroprotective effects of *Curcuma longa* and its constituents associated with Parkinson's disease

Models	Treated compounds (dose)	Challenge Health conditions	Effects	References
***In vitro* studies**				
PC12 rat cells	Curcumin (20 µmol/L)	MPP+	↑mitochondria potential, ↓ROS, ↓iNOS	Chen et al. (2006)
PC12 rat cells	Curcumin (100 nM-1 µM)	α-synuclein	↓mutant A53T, ↓cell death, ↓ROS, ↓mitochondrial depolarization, ↓cytochrome c, ↓caspase-3, caspase-9	Liu et al. (2011)
SH-SY5Y cells	Curcumin (5 µM)	α-synuclein	↓α-synuclein aggregations, ↑ α-synuclein solubility, ↓mutant α-synuclein	Pandey et al. (2008)
SH-SY5Y cells	Curcumin (140 µM)	α-synuclein	↓cytotoxicity, ↓ROS, ↓caspase-3, ↓apoptosis	Wang et al. (2010)
SH-SY5Y cells	Curcumin (5 mg/mL)	MPTP	↓behavioral impairments, ↓cell death in SN, ↓phosphorylation JNK, c-Jun	Yu et al. (2010)

Table 2.1 (continued)

Models	Treated compounds (dose)	Challenge Health conditions	Effects	References
MES23.5 cells	Curcumin (10 µmol/L)	6-OHDA	↓cytotoxicity, ↓Cu/Zn-SOD, ↓mitochondria potential, ↓ROS, ↓NF-kappaB	Wang et al. (2009)
***In vivo* studies**				
Caenorhabditis elegans	CUHNP (10, 35 µg/mL)	PD	Improved movement, ↑lifespan, slowing response, and dopamine, ↑lifespan	de Guzman et al. (2022)
Drosophila melanogaster	Curcumin (0, 125, 250, and 500 mM)	NA	↑lifespan, ↓oxidative stress, ↑locomotor activity, expression levels of age-associated genes↑	Lee et al. (2010)
Drosophila melanogaster	Curcumin (1 mM)	knockdown of dUCH	↑locomotor activity, ↓neurotoxic, ↓ROS	Nguyen et al. (2018)
Drosophila Melanogaster	Curcumin (25-50 µM)	PD	Restore low levels of dopamine	Phom et al. (2014)
Spraque-Dawley	Curcumin (50 mg/kg)	6-OHDA	↓dopamine, protected TH-positive cells in the SN	Zbarsky et al. (2005)

Table 2.1 (continued)

Models	Treated compounds (dose)	Challenge	Effects	References
		Health conditions		
Spraque-Dawley	Curcumin (80 mg/kg)	6-OHDA	↑SOD & CAT, ↓oxidative stress	Rajeswari (2006)
C57BL/6 mice	Curcumin (1.65, 3.3 g/kg/day)	MPTP	↑enzyme-glutamyl cysteine ligase, ↑glutathione, ↓CI, ↓neurotoxic ↓degeneration of SN	Mythri et al. (2011)
Wistar rats	Curcumin (50 mg/kg)	Homocysteine (Hcy)	↑locomotor activity, ↓Hcy toxicity	Mansouri et al. (2012)
Mice	Curcumin (200 mg/kg)	6-OHDA	↓nigra TH-IR neurons, TH-IR fibrils, ↑nigra dopamine, ↑glial	Tripanichkul and Jaroensuppaperch (2012)
Clinical studies				
Human	Nanomicelle curcumin (80 mg/day)	idiopathic PD	No differences in MDS-URDRS and PDQ-39	Ghodsi et al. (2022)
Human	Curcumin (2 g/day)	PD	↓clinical parameter, ↓skin α-synuclein accumulations, ↓COMPASS-31 & NMSS scores	Donadio et al. (2022)

Note NA; not available, CUHNP; Curcumin-loaded human serum albumin nanoparticles

2.3 Microencapsulated Functional Ingredients from *Curcuma longa* and its Constituents: Opportunities and Trends

2.3.1 Common Encapsulation Techniques in Food Industries

Microencapsulation is the technique of coating small entities in protective coatings (Luzzi, 1970). Microencapsulated are small spheres or irregular shapes (Gharsallaoui et al., 2007; Ghosh, 2006) or irregular shapes smaller than 1 μm or size range from 0.5-200 μm (Ghosh, 2006; Luzzi, 1970). There are 2 main components to microencapsules: the core (also known as the intrinsic part), or fill and the shell (the extrinsic part) sometimes called wall, coating, wall material, or membrane (Gharsallaoui et al., 2007), the compatibility of the core and shell materials is a crucial factor in enhancing the efficiency of microencapsulation, which microencapsulation is the process of isolating and protecting small micron-sized solid, liquid, or gas droplets from their environment by encasing them in an inert shell (Ghosh, 2006). In addition, particles of solids, liquids, and gases are encased by immersing them in a liquid phase which also contains the material that will eventually form the capsule wall, the material's coating is released when there is a need to control or prolong an action that is influenced by moisture, pH, physical force, and a combination of these factors (Luzzi, 1970). Pigments, dyes, monomers, catalysts, curing agents, flame retardants, plasticizers, and nanoparticles can all be encapsulated within the core material (Ghosh, 2006).

The benefits of microencapsulation are used to preserve the quality of sensitive substances (Jyothi et al., 2010) and unstable materials from their environments before use, improve processability (improving solubility, dispersibility, flowability), extend shelf life by preventing oxidation and dehydration, controlled release timed, protection, and compatibility of the core materials, handle toxic materials safely and conveniently, mask odor or taste, immobilize enzymes and microorganisms, control and target drug delivery (Ghosh, 2006), and to reduce the risk of drug side effects as stomach discomfort (such as aspirin) (Jyothi et al., 2010). As well as, to protect sensitive active ingredients from oxygen, water, pressure, heat, and light, food ingredients such as flavors, aromas, vitamins, minerals, spices, carotenoids, essential oils, phytochemicals,

nutritional supplements, and coenzymes are microencapsulated (Perez & Gaonkar, 2014). The design of microencapsulating products takes into account the morphology of microencapsulation as well as the material since the formation of microencapsulation requires that there be an incompatibility between the shell and the active so that a coating will exist at the surface of the active ingredient. For hydrophobic actives, a hydrophilic material such as polysaccharides (sugar, starch, glucose syrup, gum Arabic, and maltodextrin), proteins (soy, wheat, and casein), and polymers (cellulose derivatives, and chitosan), must be used to encapsulate. Lipids (such as hard fat, fatty acids, plant sterols, and glycerides), waxes (beeswax, paraffin wax, and microcrystalline wax), and polymers (shellac and ethylcellulose), which are hydrophobic actives, are used as a matrix or coating material for hydrophilic actives (Perez & Gaonkar, 2014), by the core material's contents can be released by using a permeable shell material (used for release applications), semi-permeable (used impermeable to the core material but permeable to low molecular-weight liquids), or impermeable (encloses the core material and protects it from the external environment) (Ghosh, 2006). Diffusion, permeability, or controlled-release applications all depend heavily on the size of the core material by rupturing under external pressure, melting, drying out, dissolving in a solvent, or decaying under the effect of light, the shell can release its contents (Ghosh, 2006).

Microencapsulation techniques are divided into 2 groups, namely chemical processes and physical processes, with the latter being further subdivided into physico-chemical and physico-mechanical techniques (Ghosh, 2006). Comprise spray-drying, spray chilling and spray cooling, extrusion, freeze drying, fluidized bed coating, coacervation, and liposome (Table 2.2).

2.3.1.1 Spray-drying: The food industry used the spray-drying technique the most since it is low-cost and available equipment (Balassa et al., 1971; Gharsallaoui et al., 2007). Since 1950, spray-drying encapsulation has been the first method to successfully transform liquids into powders and safeguard flavor oils against oxidation in the food industry (Gouin, 2004). The spry-drying technique consists of a 3-step process that starts with liquid atomization, moves on to gas-droplet mixing, and ends with drying from liquid droplets (Balassa et al., 1971), which produces spherical-shaped particles as a result of the liquid droplets' free suspension in a gaseous medium,

where the droplets take on a spherical shape. To encapsulate food additives, spray-drying is a technique in which the “solids phase” which could be a liquid or even volatile food flavor is combined with a capsule wall material. The solids phase usually contains a solvent or diluent (water), which is eliminated during the drying process, wherewith, the solvent or diluent liquid is dissolved, emulsified, or dispersed, and a hydrocolloid wall-former is selected from a collection of food-grade hydrocolloids (Balassa et al., 1971) and because practically all spray-drying procedures in the food industry are carried out using aqueous feed formulations, the shell material must be soluble in water to an acceptable level, limiting the number of shell materials that are accessible is a disadvantage of the spray-drying technology (Gouin, 2004).

Ullah et al. (2020) the effects of applying chia oil microcapsules (MCO) to butter on the amount of Ω-3 fatty acids, antioxidant properties, and oxidative stability were studied. MCO was made using chitosan as the encapsulating material and spray-drying at a lower temperature, the results showed that the amount of Ω-3 fatty acids in the butter was up to 8%, and the addition of MCO had no effect on the standards of butter’s identity. After 90 days of storage, the butter’s peroxide value and free fatty acid content were below the limit set by the European Union’s guidelines. There was no change in the butter’s sensory properties and has a study using spray-drying a functional oil with high amylose corn starch (HACS) to examine the effects of the microencapsulation technique. The findings released that the best microencapsulation used 28.5% functional oil, 15.75% HACS, and 57.86% of the monoglyceride content of the emulsifier (84.86%), the results showed that HACS-containing microcapsules had a good sustained release effect and that the wall material enhanced the stability of functional oil. In addition, spray-drying a functional oil with HACS allowed researchers to examine the effects of the microencapsulation technique. The revealed that the best microencapsulation used 28.5% functional oil, 15.75% HACS, and 578.6% of the monoglyceride content of the emulsifier (94.86%), the results showed that HACS-containing microcapsules had a good sustained release effect and that the wall material enhanced the stability of functional oil (Yue et al., 2020).

2.3.1.2 Spray chilling and spray cooling: Spray chilling is the process of solidifying an atomization liquid spray into particles (Oxley, 2012). In spray chilling, as opposed to spray-drying, which uses heated air, the substance to be encapsulated is

combined with the carrier and atomized by cooled or chilled air (Gibbs et al., 1999), also known as spray cooling, spray congealing, or prilling (Oxley, 2012). In the encapsulation process, an active ingredient is first dissolved in a liquid matrix before being atomized, and then the matrix hardens around the dissolved active ingredient to form a microsphere or multi-core microcapsules (Oxley, 2012), typically, vegetable oil is used as the shell material during spray cooling (45-122°C) and spray chilling using hybridized or fractionated vegetable oil (32-42°C), used to encapsulate ferrous sulfate, minerals, acidic, frozen liquids, heat sensitive material, and substance that are not soluble in common solvents (Gibbs et al., 1999). The application of spray chilling in the food and nutraceuticals industry includes flavor, vitamins, nutritional oils, probiotics (Oxley, 2012), bakery products, dry soup mixes, and food with a high fat content (Gibbs et al., 1999). Furthermore, the flavor industry uses spray cooling as an encapsulation to entrap active compounds under mid-processing conditions and to protect stability (Madene et al., 2006).

2.3.1.3 Extrusion: Extrusion is defined as the process of applying pushing force with a piston or a screw to an aperture or die is specifically designed to shape or expand the material to cause it to flow under procedures like mixing, kneading, melting, shearing, shaping, and forming (Akhtar et al., 2015; Offiah et al., 2018), use the pressure ranges from 15-200 atmospheres, maintain water in a superheated liquid state and boost shearing forces in some screw types (Akhtar et al., 2015). The extrusion, encapsulated product size that is directly formed and cut at the die is typically within the range of 0.5-1.5 mm (Harrington & Schaefer, 2014) with the raw material mass transformed into a fluid and put through a series of processes to mix and change the original ingredients into new functional forms (Akhtar et al., 2015) and the material is completely isolated by the wall material and any core is washed from the outside, which is an advantage of extrusion (Gibbs et al., 1999). In the food industry, extrusion is a practical and cost-effective technology for processing innovative foods (Akhtar et al., 2015). In this application, the main goal of the extrusion process is to create a hard, dense, glassy pellet that will protect the thoroughly mixed, encapsulated material from evaporation and oxidation for a protracted period of periodill permitting easy release of the active material when required (Harrington & Schaefer, 2014). Furthermore, extrusion is a cost-effective technique for adding leftover and by-products from food

processing back into the food (Offiah et al., 2018). The extrusion food industry's purpose: the capacity to produce a wide range of extruded products from inexpensive raw materials with short processing time, enabling uniform production through a productive and continuous system, capacity to manufacture a range of finished products (Akhtar et al., 2015; Offiah et al., 2018), environmentally friendly as a low-moisture process that does not substantially produce process effluents, in comparison to traditional baking or dough processing, the extrusion technique uses very little moisture, with typical moisture levels from 10-40% on a wet-weight basis (Akhtar et al., 2015), enhancement of shelf life by at least 2 years (Gibbs et al., 1999), and extrusion technique involves applying high temperatures for a brief period of time aperiodic-sensitive food chemicals, maybe the disadvantage of extrusion technique because used applying high temperatures (80-150°C) (Bamidele & Emmanbux, 2020).

Extrusion processing is used to make a variety of food items, such as cereals and pseudo cereals, roots and tubers, pulses and oilseeds, fruits and vegetables, and animal products (Offiah et al., 2018), example food products namely cereals that are ready to eat, snacks, dry or semi-moist pet foods, confectionery, macaroni, and products made with texturized soy protein (Akhtar et al., 2015).

In a co-rotating twin-screw extruder, the extrusion processing characteristics of yellow pea starch are influenced by various extrusion cooking processing variables, including moisture (15, 17.5, and 20%), temperature (120, 135, and 150°C), and screw speed (150, 200, and 250 rpm). Results revealed that the extrudates' radial expansion ratio value ranged from 2.52-3.63, their unit densities ranged from 0.12-0.35 g/cm^3, and their water absorption and water solubility index value ranged from 10.98-12.10 g/g and 0.12%-7.73%, respectively. The conditions with the highest expansion ratio were those with the lowest moisture content level (15%), lowest barrel temperature (120°C), and lowest screw speed (150 rpm). Additionally, the extrudates featured thick, elongated pores, and a high expansion ratio (Rangira et al., 2020). The results of this study indicate that pea starch is a good ingredient for producing puffed extruded products, however, the expansion ratio as reported above is considerably lower than the highest values found in Chinnaswamy and Hanna (1988) study, with examined corn starch extrusion cooking for expansion, the maximum expansion ratio of 16.1 was obtained when corn starch was extrusion-cooked at 140°C

barrel temperature, 14% moisture content starch, 150 rpm screw speed, 60g min^{-1} feed rate, and 3.1 L/D ratios of die-nozzle. Moreover, with moisture contents of 18.3, 26.1, and 34.8% corn starch was extrusion cooked in a twin-screw extruder at barrel temperatures of 120°C and 140°C, and screw speeds of 200, 300, and 400 rpm. The results of the investigation into the expansion characteristics of corn starch as a function of extrusion conditions were then compared, found that feed moisture content, barrel temperature, and screw speed all significantly affected the density, porosity, and expansion ratio of extruded corn starch products. Specifically, feed moisture content increases led to increases in bulk density and a decrease in porosity and expansion ratio, while increases in barrel temperature and screw speed led to a decrease in bulk density and an increase in porosity and expansion ratio (Ditudompo et al., 2016).

2.3.1.4 Freeze drying: Freeze drying also known as “lyophilization” (Hua et al., 2010) is the process of removing water from a frozen state and occurs in 2 steps, the first step is sublimation drying, at this step, most of the water in the food is removed, and the second step is the food subjected to a high vacuum, causing the water to sublimate which the majority of the unfrozen water adsorbed on the solid matrix is removed, freeze-drying is typically done a moisture level of 1-3% (Berk, 2013). The freeze-drying principle is based on the 3 stage change of water in the phase transition process of water, where solid ice can sublimate directly to gaseous water vapor within be converted to liquid water when the pressure is below the triple point at which solid, liquid, and gas coexist in thermodynamic aquarium (Liu et al., 2021). Applied examples in the food industry include meat, instant food, powder, fruit, vegetables, and fungus (Liu et al., 2021). The advantages of freeze-drying are that it preserves the original color, fragrance, flavor, and appearance of the original fresh food to the greatest extent possible, protects the composition, and avoids the loss of nutritional ingredients, is especially suitable for heat-sensitive products, the freeze-dried food can be easily reconstituted with quick rehydration speed, the freeze-dried food keeps the moisture content at a low level it is an ideal food for meals and tourism (Berk, 2013; Liu et al., 2021), the interior is porous and spongy, allowing for efficient rehydration (Liu et al., 2021), light in weight, fast soluble, and can be stored at room temperature for a prolonged period (Hua et al., 2010). Moreover, freeze-drying is time-consuming rehydration (Hua et al., 2010; Liu et al., 2021), an expensive process of dehydration

(Berk, 2013), and an energy-intensive process (Hua et al., 2010). Igual et al. (2019), the study used Midili-Kucuk and Page model to examine the water content and the presence of high molecular weight solutes on freeze-drying kinetics based on freeze-dried grapefruit formulated with high molecular weight solutes (gum Arabic and bamboo fiber) in 3 difference proportions F1 (94 g_{water}/100 g_{fresh}), F2 (80 g_{water}/100 g_{fresh}), and F3(71 g_{water}/100 g_{fresh}). The best freeze-drying kinetic model fit on grapefruit powders was Midili-Kucuk for F2 and F3, and Page for F1 and the adequate freeze-drying times for F1, F2, and F3 were 24, 16, and 18 hours, respectively. Gum Arabic and bamboo fiber present a protective effect which results in a significant antioxidant capacity due to the protection of flavonoids and antioxidant vitamins. There are also additional studies on the assessed quality of powered grapefruit products formulated with biopolymers by freeze-drying used formulation's moisture content was 90 g water/100 g mixture, which was frozen at -45°C for 48 hours, and dried at 0.05 mbar of pressure, the results show that products have a better flow behavior, greater porosity, and color more like fresh grapefruit (Egas-Astudillo et al., 2021).

2.3.1.5 Fluidized bed coating: The process of fluid bed encapsulation involves suspending solid particles in an upward-moving stream of temperature and humidity-controlled air. Once this "fluid" bed of moving particles has reached the desired temperature and is moving uniformly, it is sprayed from the top with a finely atomized liquid coating with droplets that are smaller than the substrate being coated (DeZarn, 1995). Coating materials with particles between 50-500 μm in size (Gibbs et al., 1999). Solid materials are coated with hot melt or solvent-based coatings, for hot melts, the coating hardens by solidifying in cold air, for example as fatty acids, waxes, stearines, emulsifiers, and hydrogenated vegetable oil, and for coatings based on solvents, the coating hardens by the solvent evaporating in hot air, for example as starches, gums, and maltodextrins (DeZarn, 1995; Gibbs et al., 1999; Shahidi & Han, 1993), water-soluble coatings release their contents when water is introduced, whereas hot melt components release their contents by raising the temperature or through physical breaking (Gibbs et al., 1999). There are 2 crucial processing conditions for fluid bed encapsulation, the first is the volume of fluidization air used, which regulates the height of the substrate articles within the coating region and provides adequate bed movement for uniform coating. The second is the temperature of the fluidization air

within the coating region, using the incorrect temperature or having poor temperature control will result in incomplete coverage by the coating material and subsequently produce (DeZarn, 1995). The physical properties of fluid bed technology must be investigated, materials with irregular shapes typically require structure modification to improve their shape before encapsulation, the more spherical a particle is, the better its encapsulation will be because there are no sharp edges that could protrude through the applied coating surface and become vulnerable to release, which bulk densities of less than 0.3 g/mL of material hate do be overly friable and break; during processing (DeZarn, 1995).

This technique has the advantage of being well-suited for coating materials with particle sizes larger than 50 μm. particularly with a spherical form and a relatively high specific gravity (Balassa et al., 1971). The pharmaceutical industry has used fluidized-bed coating extensively to coat particles from around 100 μm up to the size of tables, enabling sustained or controlled release, flavor mask, enteric release, and better stability, and using fluidized-bed techniques in the food industry to encapsulate additives and functional ingredients (Kuang et al., 2010). The study by Lang et al. (2020) evaluated the influence of different fluidized-bed drying temperatures at 20, 60, and 100℃ and the air speed of 2.5 m/s using a fluidized-bed dryer, on the cooking properties, *in vitro* starch digestibility, and phenolic bio accessibility of black rice, the results found that the formation of fissures in the grains dried at or above 60°C, increase in the drying temperature reduced only the caffeic acid in the free and bound fractions, on the other hand, the higher drying temperatures increased the starch digestibility and favored the extractability of the ferulic acid, and contents of all phenolic acids and anthocyanins showed a significant increase after cooking.

2.3.1.6 Coacervation: Coacervation is the word used to describe the mechanism by which lipophilic colloids salt out or phase separate into liquid droplets as opposed to solid aggregates (Madan, 1978), in colloidal chemistry, the associative phase separation process brought on by controlled changes to the media environment (pH, ionic strength, temperature, and solubility) is referred to as “coacervation” (Madan, 1978; Timilsena et al., 2019). There are 3 main mechanisms for the coacervation method to produce microcapsules: either individual coacervation droplets are drawn to and coalesce around immiscible particles in the system, or a single

coacervation droplet can encompass one or more immiscible nuclei or the microcapsule wall can be produced by molecular interaction between colloidal macromolecule particles (Madan, 1978). There are 2 types of coacervation; simple coacervation and complex coacervation, simple coacervation typically works with systems that contain just one colloidal solute (Luzzi & Gerraughty, 1964), and coacervates are produced as a result of dehydration or "water deficit" mechanisms brought on by the addition of a salt or desolvation liquid (also known as a coacervation agent or inducing agent into the reaction medium) (Madan, 1978; Timilsena et al., 2019), whereas complex coacervation typically deals with systems that contain multiple colloid solutes (Luzzi & Gerraughty, 1964) involve ionic interactions between two or more polymers with opposing charges (Timilsena et al., 2019). Given that each possesses an opposing charge at low pH, which attracts and leads to the development of an insoluble complex when combined, gelatin and gum acacia are used together (Gibbs et al., 1999). Complex coacervation is known for its ease of use, low cost, scalability, and reproducibility in the encapsulation of food ingredients that produce high encapsulation efficiency even at a very high payload, up to 99% (Timilsena et al., 2019), use encapsulation lipophilic compounds like essential oils, vegetable oils, fish oils, and palm oil (Rutz et al., 2017).

The coacervation encapsulation process includes 3 steps: the first is the creation of a system with a liquid vehicle containing the coating materials as a continuous phase and the material to be coated as a dispersed phase, the second is changing the solvent characteristics of the polymer solution to cause the wall material to phase separate, and the third is the deposition of the liquid wall material as a continuous coating about the dispersed material to create the encapsulation (Madan, 1978), which the wall material gets harder as the temperature is lowered, but it can be made softer once more by adding bases or acids, heat, or dilution (Gibbs et al., 1999). Coacervation is an effective but expensive technique (Gibbs et al., 1999), moreover, the clumping of the capsules is a disadvantage of the coacervation technique (Ghosh, 2006). In a study by Rutz et al. (2017) using the complex coacervation method to microencapsulate palm oil, which has a high carotenoid content, with chitosan/xanthan and chitosan/pectin, it was discovered that lyophilization produced particles with irregular shape and size, lower carotenoid losses, and higher yields and encapsulation efficiencies. Additionally, the release profile in both water and gastrointestinal fluid

was acceptable, and the best release profile was displayed by chitosan/pectin microparticles, following the processing the release was reduced, and the release compounds were not destroyed. The complex coacervation method was used in the study to produce functional yogurt using microparticles of orange peel extract (OPE) with high levels of polyphenolic compounds, the ratio used was 3:1, 3:2, and 3:3 for the wall materials and gum Arabic, and 1:10 and 1:20 for the OPE and wall materials, respectively. The findings showed that there were no significant influences on the physiochemical and textural characteristics of yogurt samples due to the higher 95.4% encapsulation effectiveness, which used wall materials: gum Arabic at a ratio of 3;1 and OPE:wall materials of 1:10 (El-Messery et al., 2019).

2.3.1.7 Liposome: Liposomes are single or multi-layered vesicles that completely enclose an aqueous phase inside a phospholipid-based membrane (Gulati et al., 1998; Reineccius, 1995), which therefore acts as a controlled-release particle for the active substance scattered in the lipid or aqueous phase of the particle (Reineccius, 1995). Liposome properties like permeability, stability, surface activity, and affinity can be changed by altering their size and lipid composition (Gibbs et al., 1999). Typically, liposomes range in size from 10 nm to 1 μm or more (Mishra et al., 2011) have a diameter of 25 nm to several microns, and may be freeze-dried for storage (Gibbs et al., 1999). Liposomes are structurally divided into small unilamellar vesicles (SUVs) and multilamellar vesicles (MLVs) based on the liquid bilayers (Mishra et al., 2011), and according to their size, vesicles are divided into SUVs, which are between 20-100 nm in size, large unilamellar vesicles (LUVs), which have diameter higher than 100 nm, and giant unilamellar vesicles (GUVs), which are giant vesicles with a size greater than 0.5 mm (Mishra et al., 2011; Sherry et al., 2013). Furthermore, liposome manufacturing is possible using low-cost laboratory tools (mechanical dispersion and handshaking) (Reineccius, 1995). Since liposome is composed of lipid layers is hence nontoxic and suitable for food (Gibbs et al., 1999). Various bioactive compounds, primary functional food, nutraceutical, cosmetic, and medical applications, are effectively encapsulated by liposomes (Ajeeshkumar et al., 2021; Gulati et al., 1998), although most food ingredients can be contained in liposomes, their effectiveness for flavor delivery is limited because most flavor compounds are soluble to some extent in both phases and materials that cannot be included in the liposome include those that are

insoluble in the aqueous or lipid phases or that have minimal solubility in both (Reineccius, 1995). When the protective impact of black carrot extract was examined on the stability of liposome extract loaded with lecithin content (1, 2, and 4% w/w) during storage and after 21 days of storage, the outcome showed that the samples' diameters were less than 50 nm after storage and that there was no statistically significant change and hexanal analysis was used to look at the oxidation of lipids in liposomes over 60 days. The results showed that adding the extract to liposomes could inhibit the oxidation of polyunsaturated fatty acids, that the amount of lipid should be kept to a minimum depending on the extract concentration, and that extract-loaded liposomes containing 1% lecithin provided the best oxidant protection (Guldiken et al., 2018).

Table 2.2 Principles, advantages, and disadvantages of microencapsulation techniques used in functional industries

Techniques	Advantages	Disadvantages	References
Spray-drying	1) Technology is well-established 2) Straightforward 3) Equipment is easily accessible 4) Low processing expense 5) High-yield production of capsules of excellent quality 6) Dissolve quickly 7) During the drying process, the majority of food-grade wall materials remain stable	1) Restricted amount of available shell materials 2) Wall components with low viscosities at relatively high concentration 3) The requirement to use only readily sprayable wall material solutions and dispersions 4) The active material's volatilization and deterioration 5) The active substance forming azeotropes with the solvent 6) The active substance from a surface film	Balassa et al. (1971) Gouin (2004)
Spray chilling or spray cooling	1) High output 2) Low-cost 3) It is simple to use 4) Suitable for the encapsulation of materials that wall materials' melting	1) It may be essential to handle and store materials according to particular specifications 2) Not suitable for producing water-soluble capsules	Gibbs et al. (1999) Oxley (2012)

Table 2.2 (continued)

Techniques	Advantages	Disadvantages	References
Extrusion	1) Has continuous operation and high throughput 2) Low-cost raw materials 3) Using high temperatures for a brief period of time 4) Environmentally friendly 5) Produce a variety of extruded products 6) Increase shell life for at least 2 years	1) Making of high-temperature	Akhtar et al. (2015) Offiah et al. (2018) Bamidele and Emmanbux (2020)
Freeze drying	1) Pressure the original color, fragrance, flavor, and appearance of fresh food 2) Protects the composition and avoids the loss of nutritional ingredients 3) Suitable for heat-sensitive products 4) Easily reconstituted with quick rehydration speed 5) The freeze-dried food keeps the moisture content at a low level	1) Time-consuming rehydration 2) The expensive process of dehydration 3) Energy-intensive process	Hua et al. (2010) Berk (2013) Liu et al. (2021)

Table 2.2 (continued)

Techniques	Advantages	Disadvantages	References
	6) The interior is spongy, allowing for efficient rehydration 7) Light in weight 8) Fast soluble 9) Stored at room temperature for a prolonged		
Fluidized bed coating	1) The coating of the material of particles sizes larger than 50 μm 2) Preferably having a spherical shape and relatively high specific gravity	1) Particles below 50 μm and of specific gravity tend to be swept out 2) Particles with the irregular surface are difficult to coat completely 3) Fibrous material or materials with a needle-like crystals are difficult to coat	Balassa et al. (1971)
Coacervation	1) Easy to use 2) Low cost 3) Scalability 4) Reproducibility in the encapsulation	1) The capsules' clumping 2) Expensive technique	Gibbs et al. (1999) Ghosh (2006) Timilsena et al. (2019)

Table 2.2 (continued)

Techniques	Advantages	Disadvantages	References
Liposome	1) Use low-cost laboratory tool 2) Suitable for food and non-toxic	1) The majority of flavors are somewhat soluble in both hydrophobic and hydrophilic phases	Reineccius (1995)

Microencapsulation is used in the food industry to reduce the reactivity of the core to the outside environment, to slow the rate at which the core material evaporates or transfers to the outside environment, and to facilitate easier handling of the core material (to prevent lumping, position the core material more uniformly through a mix by giving it size and outside surface like the remainder of the materials in the mix, convert a liquid to a solid form, and promote the easy mixing of the core material), to mask the core taste, dilute the core material when it is used in very small amounts, and produce uniform dispersion in the host material. In addition, controlling the release of the core material will help you create the optimum delay until the perfect stimulus (Shahidi & Han, 1993) and to supplement foods with nutrients after processing and ensure that the initial nutritional levels are not depleted over prolonged storage under the expected storage conditions (Balassa et al., 1971). The processing step in the manufacturing process of a food product may involve shear, temperature, pressure, aeration, and the addition of moisture, when the food product is processed, its storage and handling must also be taken into consideration to ensure that the previously encapsulated food ingredients will remain intact, then in the last phase, microencapsulation must be effective and release the food ingredient on time. This applies to both the development of the microencapsulation system and the creation of the microencapsulation system (Perez & Gaonkar, 2014).

The study of microencapsulated oil-soluble vitamins (A, D, and E) using a one-pot ultrasonic process, raw egg white protein, and green tea as shell material for fortifying food. After *in vitro* digestion studies show that functional vitamin D can improve vitamin D availability more than 2-fold compared to the free vitamin, and vitamin D microcapsules were highly stable and maintained their microstructures once added to staple food products (Zhu et al., 2021) and in the of potato protein (PP)-based microcapsules encapsulating grapeseed oil (GO), it was found that a GO/PP ratio of 1:2 led to the best encapsulation effect, as intact and nearly spherical microcapsules. It was also discovered that PP can be used to successfully encapsulate GO when combined with chitosan and that thermal resistance was increased in the microencapsulated GO (Wang et al., 2020).

In the study of Giovagnoli-Vicuña et al. (2022), the effects of microencapsulation on lemon extracts (LE) encapsulated with maltodextrin at 10% (M10), 20% (M20), and 30% (M30) using the freeze-dried technique were evaluated. Results showed that M30 promoted a higher microencapsulation efficiency for total phenolic content (TPC) and total flavonoid content (TFC), indicating that microencapsulated LE can be used as a functional ingredient for food supplement formulations, including using maltodextrin, gum Arabic, and inulin at 10, 20, and 30% through total phenolics, anthocyanin profile, and antioxidant activity of maqui extract on the stability of extract, the study found that 10% encapsulating polysaccharide produced the best results, with maltodextrin leading to highest efficiency improvement. While the highest levels of polyphenols 91.1% and anthocyanins 98.8% were retained after storage when maltodextrin and inulin were combined in equal amounts (Romero-González et al., 2020). Furthermore, the papaya exocarp (*Carica papaya*) rutin and trans-ferulic acid-rich extracts were evaluated for their ability to be enclosed in a pectin-alginate composite using in situ and two-step entrapment methods, the pectin: alginate ratio for gallic encapsulation was 55:45 and 61:39, resulting in 6.1 and 28.10 mg gallic acid equivalents/g capsules, which result in the highest polyphenol content than with other techniques and more controlled release triggers (Vallejo-Castillo et al., 2020).

As of November 4, 2022, while using the keyword: Microencapsulation in conjunction with the word food industry on the website www.pubmed.com. There were 285 studies discovered in total, including (a) 72 subjects for the spray-drying technique, (b) 24 subjects for the emulsion technique, (c) 18 subjects for the freeze-drying technique, (d) 15 subjects for the alginate technique, (e) 14 subjects for the coacervation technique, and (f) 23 other techniques. The most often used techniques in the food industry are the spray-drying technique, emulsion technique, and freeze-drying technique, respectively. As shown in Figure 2.8.

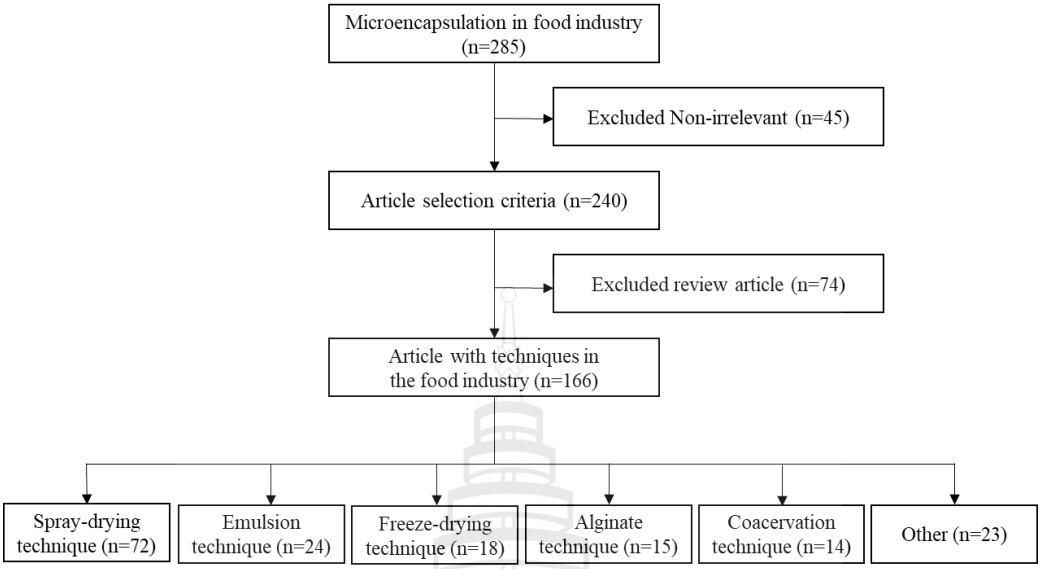


Figure 2.8 The selection process of microencapsulation techniques in the food industry by systematic review

2.3.2 The Utilization of Encapsulation Techniques in *Curcuma longa*

In the study by Wang et al. (2009) the stability of microencapsulated curcumin against light, heat, and pH was significantly improved and its solubility was greatly increased as the substance was turned into powders after the spray-drying process. The power was immediately resolved after 2 minutes, using porous starch and gelatin as the wall material in a core and wall material ratio of 1:30, the embedding temperature of 70°C, embedding time of 2 hours, inlet gas temperature of 190°C, feed flow rate of 70 mL/minutes, and drying airflow of 70 m^3/hours, the microcapsules had good encapsulation efficiency at the conditions.

The study improved the oral bioavailability and solubility of curcumin by microencapsulation. The optimal sprat drying conditions for curcumin microencapsulation were an inlet air temperature of 185°C, a feed rate of 6 mL/minute, and HICAP 100 (resistant starch) and whey protein isolate (WPI) as wall materials in a ratio of 50:50. It was discovered that curcumin microcapsules were spherical in shape with noticeable folds or dents and had diameters of 2.76. Additionally, the microcapsules showed superior thermal stability and prolonged *in vivo* release than pure curcumin and the efficiency of spray-dried curcumin ranged from 68.01 to 84.99%.

Curcumin has a 61.43% DPPH free radical scavenging activity before microencapsulation, which was largely unaltered (Patel et al., 2021).

Maltodextrin and gum Arabic were used as wall materials for freeze-dried capsules with a 1:3 maltodextrin to gum Arabic ratio to study the effects of using curcumin and the microencapsulation method on the *in vitro* release behavior of chia seed oil and its antioxidant potential during the simulated gastrointestinal tract. The results showed that adding curcumin decreased the release of chia seed oil from 44.6-37.2% on the contrary, it increased the total phenolic content of the portion of the intestine to 22 mg gallic acid equivalents/L (Fırtın et al., 2020).

Curcuma long by conventional (CSE) and supercritical fluid (SFE) extractions of curcumin resulted in microencapsulated curcumin, that was freeze-drying (-30°C) using homogeneous emulsions of maltodextrin (20 g) and gelatin (6 g) per 100 g solution modulates SD rats' hypercholesterolemia brought on by diet, the results showed that curcumin increased absorption through the gastrointestinal tract, resulting in a maximum plasma concentration of curcumin at 100 minutes of 529.31±8.73 g/mL and its stability toward metabolism in the body increased by a decrease in serum cholesterol, LDL, and triglycerides, atherogenic index (AI), and cardiac risk ratio (CRR). High-density lipoprotein (HDL) and the anti-atherogenic index (AAI) also showed a significant rise in all treated rat groups (Ashraf et al., 2022).

Curcumin can be microencapsulated in acetylated starch (AS) spherical microparticles with sizes in the range of 1-3 μm, and the encapsulation yield of curcumin can reach 96.3%. The curcumin encapsulated in AS microparticles exhibited good stability under UV irradiation at a five-fold lower dose and still retained high antioxidant activity, approximately 40% of the DPPH assay was absorbed by the curcumin encapsulated in AS microparticles after 2 minutes. These findings can be applied to the pharmacy and the food industry to extend curcumin's shelf life and allow for the controlled release of the active ingredient (Nata et al., 2014).

The results of the study on the microencapsulation of curcumin using ethanol injection and high-pressure processing (HPP) at room temperature showed that the HPP process can successfully reduce the liposome. The most effective curcumin liposomes were prepared by HPP at operational pressure of 200 MPa within 5 minutes of holding time to achieve the minimum particle size of 281.9 nm, encapsulation efficiency of

87.25%, and polydipsia after adding 0.5% of Tween 80, the particle size could be reduced to the nanoscale (70.65 nm), but the encapsulation efficiency naturally fell to 45.05% (Chen et al., 2022).

Aziz et al. (2007), studied to reduce the color staining effect and enhance the stability of curcumin via microencapsulation using the simple coacervation technique and used gelatin as the wall material in a ratio of 1:1 (curcumin of gelatin), ethanol, and acetone were used as coacervating solvents. Curcumin's intense yellow color property, which stains the fabric and skin, limits its application in dermatological preparations. According to the results, dispersing curcumin in acetone produced comparably more spherical curcumin microcapsules with a greater yield, higher curcumin loading, and higher entrapment efficiency (975.53%) than dispersing curcumin in ethanol. Additionally, the solubility of core materials microcapsules could only be formed if the core materials could be either dissolved or dispersed in the coacervating solvent and not in the aqueous polymeric solution.

The study of turmeric latte by microencapsulation turmeric oleoresin (TO) to investigate its chemical and physical properties, as well as oral bioavailability, using gum Acacia (GA), maltodextrin (MD), and dairy whitener (DW) with bio-enhancers in ratio 1:1:4. The results demonstrate that the microencapsulated powder had a dispersibility of over 95%, a wettability time below 40 seconds, and a desired curcumin content of between 539.98±6.56 and 706.40±5.25 mg/100 g. Additionally, the turmeric latte demonstrated a stronger antioxidant activity with 4.2; fold-improved permeability through non-everted rat gut and 4.9-fold higher oral bioavailability in rats, all off-supported enhancement (Ipar et al., 2022).

Table 2.3 Microencapsulation techniques used in *Curcuma longa*

Techniques	Materials	Ratio of material	Temperature	Encapsulation efficiency	Size	References
Spray-drying	Porous starch and gelatin	1:30	190°C	98.40%	NA	Wang et al. (2009)
Spray-drying	HICAP 100 (resistant starch) and whey protein isolate	50:50	185°C	68.02-84.99%	2.76 µm	Patel et al. (2021)
Freeze-drying	Maltodextrin and gum Arabic	1:3	-80°C	66.69%	NA	Fırtın et al. (2020)
Freeze-drying	Maltodextrin and gelatin	NA	-30°C	NA	NA	Ashraf et al. (2022)
Spray drying	Acetylated starch	NA	60°C	96.3	1-3 µm	Nata et al. (2014)
Liposome	NA	NA	Room temperature	87.25%	281.9 nm	Chen et al. (2022)
Coacervation	Gelatin	1:1	-70°C	75.53%	83.68 µm	Aziz et al. (2007)
Spray-drying	Gum acacia, maltodextrin, and dairy whitener	1:1:4	140°C	95.15%	325.93 nm	Ipar et al. (2022)

Note NA; Non-applicable

CHAPTER 3

METHODOLOGY

3.1 A Screening Strategy of Potential Neuroprotective Agents from Medicinal Plants

A systematic review-based approach for screening promising plant-based antioxidants as functional ingredients from the list of Thai FDA-approved dietary supplements obtained from medicinal plants was employed as described in Figure 3.1. The list of Thai FDA-approved dietary supplements obtained from plant-based antioxidants has described the details of 211 plant-based antioxidants that could be used as dietary supplements. The systematic review-based approach was conducted with the following inclusion criteria:

(I) To assess the sustainability of plant extracts as local ingredients, the chosen plant-based antioxidants must be cultivable in Thailand (Table A1).

(II) Several studies have conclusively demonstrated that antioxidants play an important role in neuroprotection. As a result, the preliminary antioxidant activity of the chosen medicinal plants must be reported (Table 3.1).

(III) The results obtained from the valid, accurate, simple, and inexpensive methods of evaluating radical scavenging activity, 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay and 2,2'-casino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay were included for data analysis. The medicinal plants were selected based on the correlation been DPPH and ABTS data (Figure A1) and reports of the inhibitory effects of acetylcholinesterase (AChE). To demonstrate the neuroprotective properties of plant-based antioxidants (Table 3.2).

(IV) Only commercially accessible extracts were included in the subsequent experiments to ensure that the chosen plant-based antioxidants could be used in functional food sectors (Table A2). Therefore, 21 plant-based antioxidants were employed in the following methods.

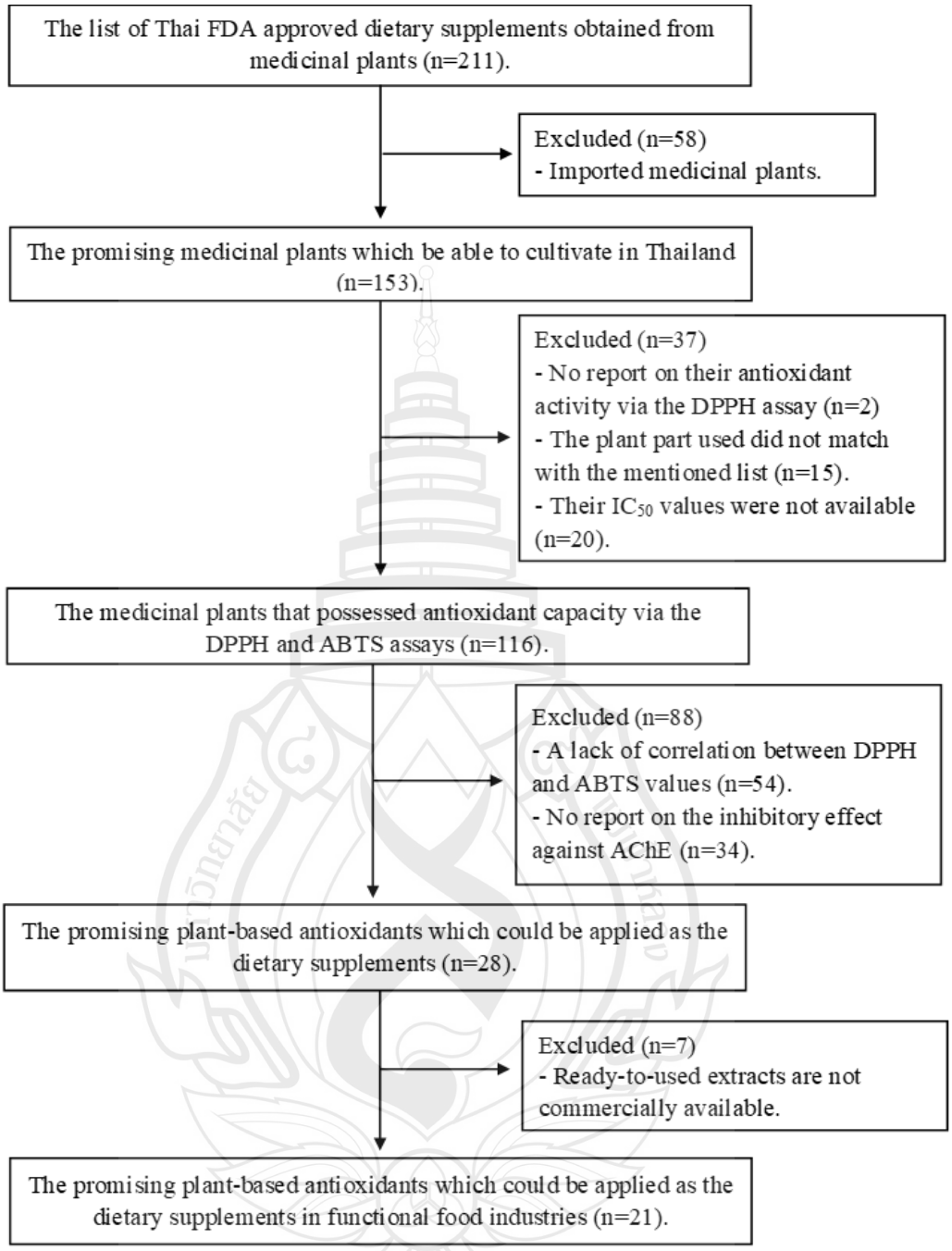


Figure 3.1 The flow diagram for the systematic review-based approach to screening the antioxidant capacities of Thai FDA-approved dietary supplements derived from plant-based antioxidant

Table 3.1 Reported antioxidant capacities of plant-based antioxidants chosen from the list of Thai FDA-approved dietary supplements derived from medicinal plants

No	Scientific name	Antioxidant capacities (IC_{50}; mg/mL)		References
		DPPH	ABTS	
1	*Actinidia chinensis*	0.20	0.02	Bekhradnia et al. (2011) Salama et al. (2018)
2	*Aegle marmelos*	0.06	0.02	Rajan et al. (2011)
3	*Allium cepa*	161.29	0.67	Dash et al. (2021) Ye et al. (2013)
4	*Allium fistulosum*	0.01	0.05	Chang et al. (2013) Zhao et al. (2012)
5	*Allium sativum*	0.20	0.44	Kim et al. (2016)
6	*Aloe vera*	0.003	0.003	Mazzulla et al. (2012) Uddin et al. (2020)
7	*Alpinia galangal*	10.66	0.09	Mahae and Chaiseri (2009) Srividya et al. (2010)
8	*Ananas comosus*	0.0001	0.0500	Fidrianny et al. (2018) Putri et al. (2018)
9	*Angelica polymorpha*	0.01	0.10	Makchuchit et al. (2010) Li et al. (2007)
10	*Antidesma ghaesembilla*	0.11	0.02	Gargantiel and Ysrael (2014)
11	*Apium graveolens*	1.09	0.71	Uddin et al. (2015)
12	*Bacopa monnieri*	0.79	1.11	Moreno-Escobar et al. (2011)
13	*Beta vulgaris*	1.38	0.66	Alonzo-Macías et al. (2020) Al-Sama et al. (2020)
14	*Boesenbergia rotunda*	0.74	0.06	Mat Yasin et al. (2018)
15	*Brassica oleracea*	0.74	16.95	Leamsamrong et al. (2019) Khongrum et al. (2021)
16	*Brassica oleracea*	15.71	17.04	Yang et al. (2015)
17	*Brassica oleracea*	3.72	0.04	Chaudhary et al. (2018) Sri Agustini and Agustini (2017)
18	*Calendula officinalis*	0.10	0.01	Preethi et al. (2006)
19	*Camellia sinensis*	0.010	0.006	Pereira et al. (2014)
20	*Capsicum annuum*	0.004	0.070	Loizzo et al. (2015)

Table 3.1 (continued)

No	Scientific name	Antioxidant capacities (IC_{50}; mg/mL)		References
		DPPH	ABTS	
21	*Capsicum annuum* (peppers)	0.03	0.04	Olatunji and Afolayan (2019)
22	*Capsicum frutescens*	0.020	0.003	Olatunji and Afolayan (2019)
23	*Carthamus tinctorius*	0.07	0.08	Sun et al. (2020)
24	*Centella asiatica*	0.05	0.03	Mohapatra et al. (2021)
25	*Chaenomeles speciosa*	0.22	16.03	Tian et al. (2015) Turkiewicz et al. (2020)
26	*Chrysanthemum indicum*	2.21	0.20	Youssef et al. (2020) Yuan et al. (2019)
27	*Chrysanthemum morifolium*	1.69	2.13	Gong et al. (2019)
28	*Cinnamomum cassia*	0.040	0.005	Brodowska et al. (2016)
29	*Cinnamomum verum*	0.01	0.01	Gulcin et al. (2019)
30	*Citrus aurantifolia*	2.36	0.26	Lin et al. (2019)
31	*Citrus* x *aurantium*	0.81	0.49	Zeghad et al. (2019)
32	*Citrus limon*	0.03	0.03	Loizzo et al. (2019)
33	*Citrus reticulate*	0.72	1.26	Singanusong et al. (2014)
34	*Citrus sinensis*	29.70	4.17	Lin et al. (2021)
35	*Cocos nucifera*	0.29	0.01	Siramon et al. 2020
36	*Coffea arabica*	0.16	0.36	Kaisangsri et al. (2019)
37	*Coix lacryma-jobi*	17.56	21.20	Yuan et al. (2014) Wu et al. (2018)
38	*Cucumis melo*	0.02	17.56	Widowati (2015) Hayet et al. (2016)
39	*Cucurbita pepo*	0.03	0.01	Thangavel et al. (2019)
40	*Curcuma longa*	0.001	0.020	Tanvir et al. (2017) Mošovská et al. (2016)
41	*Cymbopogon citratus*	0.03	0.17	Salaria et al. (2020)
42	*Cynara scolymus*	0.910	0.007	Kollia et al. (2017) Bueno-Gavilá et al. (2021)
43	*Daucus carota*	1.36	1.58	Servi et al. (2021)

Table 3.1 (continued)

No	Scientific name	Antioxidant capacities (IC_{50}; mg/mL)		References
		DPPH	ABTS	
44	*Fragaria* x *ananassa*	0.0004	0.0400	Soulef et al. (2020)
45	*Ganoderma lucidum*	0.050	0.001	Tel et al. (2015)
46	*Garcinia atroviridis*	0.630	0.006	Chatatikun et al. (2020)
47	*Garcinia mangostana*	0.07	0.09	Mohammad et al. (2019)
48	*Ginkgo biloba*	0.002	0.130	Qa'dan et al. (2011) Li et al. (2021)
49	*Glycine max*	0.11	0.08	Prahastuti et al. (2019)
50	*Glycyrrhiza uralensis*	0.05	0.05	Fan et al. (2014)
51	*Gynostemma pentaphyllum*	0.06	0.07	Wang et al. (2018)
52	*Helianthus annuus*	0.09	0.08	Islam et al. (2016) Kusmiati et al. (2021)
53	*Helianthus tuberosus*	0.16	0.10	Mariadoss et al. (2021)
54	*Hibiscus sabdariffa*	0.01	0.02	Yang et al. (2012)
55	*Hippophae rhamnoides*	0.1200	0.0008	Kant et al. (2012)
56	*Hordeum vulgare*	0.04	0.01	Boubakri et al. (2017)
57	*Houttuynia cordata*	0.10	0.42	Tuyen et al. (2018)
58	*Illicium verum*	0.0005	0.0007	Rao et al. (2012)
59	*Ipomoea aquatica*	0.39	0.39	Malakar and Choudhury (2015)
60	*Kaempferia parviflora*	1.14	1.46	Choi et al. (2018)
61	*Lentinula edodes*	0.05	0.02	Elhusseiny et al. (2021)
62	*Linum usitatissimum*	0.05	0.05	Han et al. (2018)
63	*Lonicera japonica*	0.01	0.02	Fan et al. (2019)
64	*Lycium barbarum*	1.29	0.39	Skenderidis et al. (2018)
65	*Lycopersicon esculentum*	0.21	0.05	Kim et al. (2009)
66	*Malus domestica*	0.0004	0.0002	Fidrianny et al. (2017)
67	*Matricaria chamomilla*	0.001	0.001	Hajaji et al. (2017)
68	*Medicago sativa*	0.10	0.01	Rana et al. (2010)
69	*Melissa officinalis*	0.010	0.001	Rădulescu et al. (2021)

Table 3.1 (continued)

No	Scientific name	Antioxidant capacities (IC_{50}; mg/mL)		References
		DPPH	ABTS	
70	*Mentha* x *piperita*	0.01	0.15	Nickavar et al. (2008)
71	*Mentha spicata*	0.09	0.17	Nickavar et al. (2008)
72	*Momordica cochinchinensis*	143.50	0.03	Ismail et al. (2019) Wimalasiri (2015)
73	*Momordica grosvenorii*	0.11	1.47	Liu et al. (2018)
74	*Moringa oleifera*	1.87	1.36	Xu et al. (2019)
75	*Morus alba*	6.65	1.40	Thabti et al. (2013)
76	*Musa sapientum*	0.050	0.002	Dahham et al. (2015) Fidrianny et al. (2014)
77	*Myrciaria dubia*	0.05	0.02	Castro et al. (2018)
78	*Ocimum basilicum*	0.59	0.73	Sriram et al. (2019)
79	*Opuntia ficus-indica*	3.52	0.80	Zeghad et al. (2019)
80	*Origanum vulgare*	0.10	0.09	Kaska (2018)
81	*Oryza sativa*	1.09	2.80	Surin et al. (2020)
82	*Paeonia lactiflora*	0.61	0.34	Meng et al. (2021)
83	*Panicum miliaceum*	0.21	0.69	Ghimire et al. (2019)
84	*Persea americana*	0.010	0.001	Antasionasti et al. (2017)
85	*Petroselinum crispum*	281.02	587.98	Yu et al. (2021)
86	*Phaseolus mungo*	488.00	1.12	Saeed et al. (2020) Khatun and Kim (2021)
87	*Phaseolus vulgaris*	0.002	0.010	Abdulrahman et al. (2021)
88	*Phyllanthus emblica*	0.05	0.30	Charoenteeraboon et al. (2010)
89	*Pinus massoniana*	0.05	0.06	Ferreira-Santos et al. (2020)
90	*Piper nigrum*	0.20	0.22	Akbar et al. (2014)
91	*Piper sarmentosum*	0.26	0.18	Nguyen et al. (2020)
92	*Pisum sativum*	0.65	1.90	Hadrich et al. (2014)
93	*Pleurotus ostreatus*	0.04	0.01	Elhusseiny et al. (2021)
94	*Plukenetia volubilis*	0.04	0.04	Wuttisin et al. (2020)
95	*Prunus armeniaca*	83.86	0.47	Bonesi et al. (2018)
96	*Prunus cerasus*	10.96	0.31	Becker et al. (2019)
97	*Prunus domestica*	0.0900	0.0005	Bonesi et al. (2018)

Table 3.1 (continued)

No	Scientific name	Antioxidant capacities (IC_{50}; mg/mL)		References
		DPPH	ABTS	
98	*Prunus mume*	0.005	0.020	Xia et al. (2010)
99	*Punica granatum*	0.45	72.73	Bopitiya and Madhujith (2015)
100	*Rosa centifolia*	0.92	0.07	Yi et al. (2019)
101	*Rosmarinus officinalis*	0.10	0.18	Karadağ et al. (2019)
102	*Rubus fruticosus*	3.53	0.50	Kukrić et al. (2020)
103	*Rubus idaeus*	0.040	0.004	Veljković et al. (2019)
104	*Saccharum officinarum*	19.82	3.50	Motham et al. (2020)
105	*Salvia hispanica*	0.001	0.001	Hernández-Pérez et al. (2020)
106	*Sesamum indicum*	8.88	24.91	Ruslan et al. (2018)
107	*Solanum torvum*	0.02	0.01	Magalhães et al. (2014)
108	Tagetes erecta	0.06	0.07	Kusmiati et al. (2021)
109	*Terminalia chebula*	0.002	0.003	Sasidharan et al. (2012)
110	*Thymus vulgaris*	0.01	0.05	Köksal et al. (2016)
111	*Trigonella-foenum*	0.35	0.10	Priya et al. (2011)
112	*Triticum aestivum*	0.05	0.01	Abeysekera et al. (2017)
113	*Vaccinium macrocarpon*	0.09	0.10	Kalin et al. (2015)
114	*Vitis vinifera*	0.27	0.04	Zeghad et al. (2019)
115	*Vigna radiata*	0.07	0.08	Basha and Rao (2017)
116	*Zingiber officinale*	0.008	0.007	Ali et al. (2018)

Table 3.2 Inhibitory effect against acetylcholinesterase of plant-based antioxidants

No	Scientific name	Acetylcholinesterase (AChE)		References
		IC_{50} (mg/mL)	%inhibition (Conc.)	
1	*Actinidia chinensis*	ND	79.8 (1 mg/mL)	Hwang et al. (2017)
2	*Aegle marmelos*	ND	44.65 (0.1 mg/mL)	Ingkaninan et al. (2003)
3	*Allium cepa*	0.07	ND	Nile et al. (2018)
4	*Allium fistulosum*	ND	21.31 (1 mg/mL)	Suttisansanee et al. (2021)
5	*Allium sativum*	ND	3.02 (0.1 mg/mL)	Ingkaninan et al. (2003)
6	*Aloe vera*	0.05	89.82 (0.1 M)	Shaker (2019)
7	*Alpinia galangal*	0.03	ND	Chaiyana et al. (2022)
8	*Ananas comosus*	ND	9.30 (1 mg/mL)	Nanasombat et al. (2019)
9	*Angelica polymorpha*	ND	68.58 (50 µL)	Wang et al. (2017)
10	*Antidesma ghaesembill*	NA	NA	
11	*Apium graveolens*	ND	4.70 (10 µL)	Gholamhoseinian et al. (2009)
12	*Bacopa monnieri*	0.52	15.15 (1 mg/mL)	Mathew et al. (2014)
13	*Beta vulgaris*	0.0012	92.90 (100 µM)	Rehman et al. (2022)
14	*Boesenbergia rotunda*	ND	70.10 (20 µL)	Abdelwahab et al. (2013)
15	*Brassica oleracea*	NA	NA	
16	*Brassica oleracea*	NA	NA	
17	*Brassica oleracea*	NA	NA	
18	*Calendula officinalis*	ND	5.23 (500 µg/mL)	Ercetin et al. (2012)
19	*Camellia sinensi*	ND	81.66 (2 mg/mL)	Suttisansanee et al. (2019)
20	*Capsicum annuum*	0.08	ND	Loizzo et al. (2008)
21	*Capsicum annuum*	ND	15.80 (5 mg/ mL)	Nantakornsuttanan et al. (2016)
22	*Capsicum frutescens*	NA	NA	
23	*Carthamus tinctorius*	ND	30.33 (0.1 mg/mL)	Ingkaninan et al. (2003)
24	*Centella asiatica*	ND	3.24 (1 mg/mL)	Nanasombat et al. (2019)
25	*Chaenomeles speciosa*	NA	NA	
26	*Chrysanthemum indicum*	0.03	ND	Lim et al. (2007)
27	*Chrysanthemum morifolium*	NA	NA	
28	*Cinnamomum cassia*	NA	NA	
29	*Cinnamomum verum*	ND	0.5 (10 µL)	Gholamhoseinian et al. (2009)
30	*Citrus aurantifolia*	0.02	ND	Jazayeri et al. (2014)
31	*Citrus* x *aurantium*	0.15	ND	Tundis et al. (2012)
32	*Citrus limon*	0.85	ND	Aazza et al. (2011)
33	*Citrus reticulate*	NA	NA	
34	*Citrus sinensis*	ND	30.89 (16.67 mL/L)	Ademosun and Oboh (2012)
35	*Cocos nucifera*	NA	NA	

Table 3.2 (continued)

No	Scientific name	Acetylcholinesterase (AChE)		References
		IC_{50} (mg/mL)	**%inhibition (Conc.)**	
36	*Coffea arabica*	ND	0.95 (200 µL)	Shen et al. (2022)
37	*Coix lacryma-jobi*	ND	0.38 (850 µg/mL)	Shwetha et al. (2019)
38	*Cucumis melo*	NA	NA	
39	*Cucurbita pepo*	NA	NA	
40	*Curcuma longa*	0.06	96.50 (0.5 mM)	Abbasi et al. (2012)
41	*Cymbopogon citratus*	ND	12.40 (0.2 mg/mL)	Suttisansanee et al. (2021)
42	*Cynara scolymus*	0.09	ND	Turkiewicz et al. (2019)
43	*Daucus carota*	13.13	ND	Yusuf et al. (2021)
44	*Fragaria* x *ananassa*	0.02	77.68 (500 µg/mL)	Mahnashi and Alshehri (2022)
45	*Ganoderma lucidum*	ND	32.50 (1 mg/mL)	Cör et al. (2017)
46	*Garcinia atroviridis*	0.03	80.15 (100 µg/mL)	Tan et al. (2014)
47	*Garcinia mangostana*	ND	13.79 (1 mg/mL)	Nanasombat et al. (2019)
48	*Ginkgo biloba*	ND	8.08 (1 mg/mL)	Nanasombat et al. (2019)
49	*Glycine max*	NA	NA	
50	*Glycyrrhiza uralensis*	NA	NA	
51	*Gynostemma pentaphyllum*	ND	19.64 (2 mg/mL)	Suttisansanee et al. (2019)
52	*Helianthus annuus*	NA	NA	
53	*Helianthus tuberosus*	ND	5.51 (1 mg/mL)	Nanasombat et al. (2019)
54	*Hibiscus sabdariffa*	ND	19.05 (2 mg/mL)	Suttisansanee et al. (2019)
55	*Hippophae rhamnoides*	ND	75.85 (50 µg/mL)	Wang et al. (2022)
56	*Hordeum vulgare*	ND	0.71 (35 µL)	Kobus-Cisowska et al. (2020)
57	*Houttuynia cordata*	0.08	ND	Huh et al. (2014)
58	*Illicium verum*	0.06	ND	Bhadra et al. (2011)
59	*Ipomoea aquatica*	0.17	62.54 (400 µg/mL)	Dhanasekaran et al. (2015)
60	*Kaempferia parviflora*			
61	*Lentinula edodes*	NA	NA	
62	*Linum usitatissimum*	NA	NA	
63	*Lonicera japonica*	NA	NA	
64	*Lycium barbarum*	ND	0.71 (25 µL)	Mocan et al. (2018)
65	*Lycopersicon esculentum*	5.70	ND	Oboh et al. (2015)
66	*Malus domestica*	ND	5.87 (1 mg/mL)	Nanasombat et al. (2019)
67	*Matricaria chamomilla*	0.60	ND	Başı et al. (2016)
68	*Medicago sativa*	0.02	ND	Eruygur et al. (2018)

Table 3.2 (continued)

No	Scientific name	Acetylcholinesterase (AChE)		References
		IC_{50} (mg/mL)	%inhibition (Conc.)	
69	*Melissa officinalis*	ND	1.72 (25 µL)	Dastmalchi et al. (2018)
70	*Mentha* x *piperita*	ND	4.2 (10 µL)	Gholamhoseinian et al. (2009)
71	*Mentha spicata*	0.02	ND	Ali-Shtayeh et al. (2019)
72	*Momordica cochinchinensis*	ND	9.17 (1 mg/mL)	Nanasombat et al. (2019)
73	*Momordica grosvenorii*	NA	NA	
74	*Moringa oleifera*	0.21	ND	Nwidu et al. (2018)
75	*Morus alba*	ND	4.24 (1 mg/mL)	Nanasombat et al. (2019)
76	*Musa sapientum*	ND	24.19 (0.1 mg/mL)	Ingkaninan et al. (2003)
77	*Myrciaria dubia*	1.57	ND	Ramirez and Carazzone (2022)
78	*Ocimum basilicum*	0.65	ND	Singh et al. (2016)
79	*Opuntia ficus-indica*	0.78	ND	Ressaissi et al. (2016)
80	*Origanum vulgare*	0.003	95.61 (250 µg/mL)	de Torre et al. (2022)
81	*Oryza sativa*	ND	13.27 (1 mg/mL)	Nanasombat et al. (2019)
82	*Paeonia lactiflora*	NA	NA	
83	*Panicum miliaceum*	NA	NA	
84	*Persea americana*	NA	NA	
85	*Petroselinum crispum*	ND	21.00 (0.1 mg/mL)	Adsersen et al. (2006)
86	*Phaseolus mungo*	NA	NA	
87	*Phaseolus vulgaris*	NA	NA	
88	*Phyllanthus emblica*	ND	17.36 (1 mg/mL)	Nanasombat et al. (2019)
89	*Pinus massoniana*	NA	NA	
90	*Piper nigrum*	ND	58.02 (0.1 mg/mL)	Ingkaninan et al. (2003)
91	*Piper sarmentosum*	ND	73.61 (100 µg/mL)	Werawattanachai and Kaewanatowong (2019)
92	*Pisum sativum*	ND	32.00 (100 µg/mL)	Mejri et al. (2019)
93	*Pleurotus ostreatus*	1.75	ND	Chamutpong et al. (2019)
94	*Plukenetia volubilis*	NA	NA	
95	*Prunus armeniaca*	0.45	ND	Vahedi-Mazdabadi et al. (2020)
96	*Prunus cerasus*	NA	NA	Cásedas et al. (2016)
97	*Prunus domestica*	18.07	ND	Rybak and Wojdyło, (2023)
98	*Prunus mume*	NA	NA	
99	*Punica granatum*	0.08	62.4 (1 mg/mL)	Mathew et al. (2014)
100	*Rosa centifolia*	NA	NA	
101	*Rosmarinus officinalis*	ND	17.00 (0.1 mg/mL)	Adsersen et al. (2006)

Table 3.2 (continued)

No	Scientific name	Acetylcholinesterase (AChE)		References
		IC_{50} (mg/mL)	**%inhibition (Conc.)**	
102	*Rubus fruticosus*	331.02	47.82 (320 mg/mL)	Akyüz et al. (2022)
103	*Rubus idaeus*	NA	NA	
104	*Saccharum officinarum*	NA	NA	
105	*Salvia hispanica*	0.02	38.82 (10 µg/mL)	Kocakaya et al. (2020)
106	*Sesamum indicum*	ND	66.17	Kim et al. (2023)
107	*Solanum torvum*	ND	1.8 (50 µL)	Senizza et al. (2021)
108	Tagetes erecta	1.13	ND	Moliner et al. (2018)
109	*Terminalia chebula*	0.19	41.06 (1 mg/mL)	Mathew et al. (2014)
110	*Thymus vulgaris*	0.22	ND	Aazza et al. (2011)
111	*Trigonella-foenum graecum*	ND	6.00 (1 mg/mL)	Mathew et al. (2014)
112	*Triticum aestivum*	NA	NA	
113	*Vaccinium macrocarpon*	NA	NA	
114	*Vitis vinifera*	ND	3.86 (1 mg/mL)	Tkacz et al. (2019)
115	*Vigna radiata*	NA	NA	
116	*Zingiber officinale*	ND	0.6 (10 µL)	Gholamhoseinian et al. (2009)

Note ND; No data available, NA; Not active

3.2 Medicinal Plant Extracts

21 extract of medicinal plants were purchased from AP Operations Co.,Ltd. (Chonburi, Thailand), as shown in Table A3, using plant parts that the FDA authorized for use in dietary supplements.

3.3 Evaluation of *in vitro* Antioxidant Capacities and Chemical Markers

3.3.1 Quantification of Proposed Chemical Markers for Antioxidant Activity

3.3.1.1 Total phenolic content (TPC)

The TPC in the studied samples was measured based on the Folin-Ciocalteu method according to the previously published method with few modifications. In brief, one mL of 10-fold dilution Folin-Ciocalteu reagent was well mixed with the extract (1 mg/mL; 100 µL) followed by the addition of sodium carbonate solution (80 µL; 20% w/v). The solution was properly mixed and then held in the dark at room temperature for 45 minutes before the absorbance at 630 nm was measured. The TPC was expressed as milligrams of gallic acid equivalent per gram of extract (mg gallic acid equivalent/ g of extract). Calculate the value and input the results into the formula to determine the solution's concentration based on the graph:

$$y = mx + c$$

where x represents the sample solution's concentration

y represents the sample solution's absorbance

by using the formula $y = Abs_{sample} - Abs_{blank}$, where m and c are constants derived from the linear graph showing the correlation between the value of gallic acid and the absorbance 630 nm.

3.4.1.2 Total flavonoid content (TFC)

The TFC of each extract was evaluated by the modified aluminum chloride colorimetric method. Briefly, the tested solution was made by mixing 20 µL of the extract (1 mg/mL), 80 µL of distilled water, and 6 µL of 5% (w/v) of sodium nitrite. The mixture was incubated for 6 minutes at room temperature after that 6 µL of 10% (w/v) aluminium trichloride and then was incubated for 6 minutes at room temperature again. This reaction was stopped by adding 40 µL of sodium hydroxide (1 M). The final volume of the mixture was adjusted to 48 µL with sterile-

distilled water. The absorbance was taken at 510 nm against the reagent blank. The TFC was calculated from a calibration curve using catechin standard flavonoid, and the result was mentioned as milligrams of catechin equivalent per gram of extract (mg catechin equivalent/ g of extract). Calculate the value and input the results into the formula to determine the solution's concentration based on the graph:

$$y = mx + c$$

where x represents the sample solution's concentration

y represents the sample solution's absorbance

by using the formula $y = Abs_{sample} - Abs_{blank}$, where m and c are constants derived from the linear graph showing the correlation between the value of catechin and the absorbance 510 nm.

3.3.2 Metal Chelating Assay (MCA)

The existence of excess transition metals, such as iron (Fe) and copper (Cu), has been thoroughly documented in terms of triggering Fenton and Haber-Weiss reactions and the generation of ROS. To evaluate the metal chelating property of the extracts, the ferrous ion chelating (FIC) assay was employed using a previously established approach (Cherrak et al., 2016). 63 µL of each plant extract at varying concentrations (2-fold dilution) ranging from 1.0-0.016 mg/mL were combined with 95% ethanol and 2 mM iron (II) chloride (6.3 µL). The reaction was started by adding 5 mM of ferrozine (12.5 µL) and incubated for 10 minutes at room temperature. The increase in absorbance of the stable ferrous-ferrozine complex was detected at 562 nm. As a positive control, ethylenediaminetetraacetic acid (EDTA) was utilized. The metal chelating activity (MCA) of plant-based antioxidants was quantified as the amounts that inhibited the ferrous ion ferrozine complex by %inhibition was estimated as follows:

$$\%\text{inhibition} = \frac{Abs_{control} - (Abs_{sample} - Abs_{blank}) \times 100}{Abs_{control}}$$

$Abs_{control}$ is the absorbance of 63 µL 95% ethanol, 6.3 µL $FeCl_2$ solution, and 12.5 µL Ferrozine

Abs_{sample} is the absorbance of 63 µL extract, 6.3 µL $FeCl_2$ solution, and 12.5 µL Ferrozine

Abs_{blank} is the absorbance of 63 µL extract, 6.3 µL Distilled water, and 12.5 µL Ferrozine

3.3.3 Chain-breaking Antioxidant Capacities

Different techniques have been used to elucidate the free radical scavenging potential of the chosen plant-based antioxidants including mixed-mode-based assays (DPPH and ABTS scavenging activities), single electron transfer mechanism-based assays (ferric reducing antioxidant power assay and superoxide anion radical scavenging assay), and hydrogen atom transfer-based assay (peroxyl radical scavenging capacity).

3.3.3.1 DPPH radical scavenging activity

The mixed-mode colorimetric procedures, DPPH radical scavenging assays were carried out as previously described (Chanthasri et al., 2018; Wetchakul et al., 2019). To test the ability of the extracts in scavenging DPPH radical, an aliquot (20 µL) of the sample at concentrations ranging from 1.0-0.002 mg/mL was placed on a 96-well plate containing 80 M DPPH in ethanol solution (180 µL) to examine the extracts' ability to scavenge DPPH radical. The plate was carefully stirred and incubated in the dark for 5 minutes at room temperature. At 490 nm, the absorbance of the solution was measured. The scavenging activity of the extracts was expressed as the percentage inhibition of DPPH. The percentage of $DPPH^+$ based-scavenging activities was calculated using the equation below:

$$\%\text{inhibition} = \frac{Abs_{control} - (Abs_{sample} - Abs_{blank})}{Abs_{control}} \times 100$$

$Abs_{control}$ is the absorbance of 20 µL 95% ethanol, and 180 µL DPPH solution

Abs_{sample} is the absorbance of 20 µL extract, and 180 µL DPPH solution

Abs_{blank} is the absorbance of 20 µL extract, and 180 µL methanol

3.3.3.2 ABTS radical scavenging activity

The mixed-mode colorimetric procedures, ABTS radical scavenging assays were carried out as previously described (Chanthasri et al., 2018; Wetchakul

et al., 2019). The $ABTS^+$ radicals were generated by combining an aliquot of ABTS solution (2 mM) and potassium persulfate solution (2.45 mM) in a 1:1 volume ratio and allowed to stand in the dark at room temperature for 16 hours. The absorbance of the $ABTS^+$ solution was adjusted to 0.70±0.02 at 734 nm with ethanol. A two-fold serial dilution (20 µL) of each extract at concentrations ranging from 1.0-0.002 mg/mL was added into 200 µL of $ABTS^+$ solution. After 6 minutes of incubation at room temperature, the absorbance of each sample was measured at 734 nm. Trolox was used as a reference antioxidant. The scavenging activity of the extracts was expressed as the percentage inhibition of ABTS. The percentage of $ABTS^+$ based-scavenging activities was calculated using the equation below:

$$\%\text{inhibition} = \frac{Abs_{control} - (Abs_{sample} - Abs_{blank})}{Abs_{control}} \times 100$$

$Abs_{control}$ is the absorbance of 20 µL 95% ethanol, and 200 µL $ABTS^+$ solution

Abs_{sample} is the absorbance of 20 µL extract, and 200 µL $ABTS^+$ solution

Abs_{blank} is the absorbance of 20 µL extract, and 200 µL PBS solution

3.4.3.3 Ferric reducing antioxidant power (FRAP)

Ferric reducing antioxidant power were employed based on the single electron transfer mechanisms. The FRAP values of the extracts were recorded based on the reduction of the ferric-tripyridyl triazine complex to ferrous-TPTZ by electron donating antioxidants (Rajurkar & Hande, 2011). The FRAP working solution was freshly prepared by mixing 10 mL of 300 mM acetate buffer, 1 mL of 10 mM TPTZ solution, and 1 mL of 20 mM ferric chloride. An aliquot of 20 µL of the extracts (1 mg/mL) was mixed with 180 µL of the FRAP reagent and incubated for 30 minutes in the dark. The level of the ferrous-TPTZ complex was monitored at 593 nm. FRAP values were expressed as micromoles of ferrous per milligram of extract (µM Fe_2SO_4/mg extract). Calculate the molar value of ferrous sulfate produced by substituting the absorbance value into the linear equation based on the standard graph:

$$y = mx + c$$

where x represents the ferrous sulfate solution's concentration

y represents the sample solution's absorbance

by m and c are constants derived from the linear graph showing the correlation between the value of ferrous sulfate and the absorbance of 593 nm.

3.3.3.4 Nitro blue tetrazolium assay (NBT)

Superoxide anion radicals were employed based on the single electron transfer mechanisms, generated by the riboflavin/methionine/illuminate system and quantified by the nitro blue tetrazolium assay (de Vargas et al., 2016; Wetchakul et al., 2019). The reaction mixture contained 30 µL of NBT (200 µg/mL) and 90 µL of the solution consisting of a mixture of riboflavin (30 µg/mL), methionine (30 µg/mL), Ethylenediaminetetraacetic acid (EDTA) (20 µg/ mL), and the plant extract at different concentration (2-fold dilution; 1.0-0.002 mg/mL) diluted in 0.05 M phosphate buffer, pH 7.4. The absorbance was recorded at 560 nm after incubation with illumination of fluorescent lamps (20 W) at 25°C for 25 minutes. The absorbance of formazan dye in the presence of the extracts, or catechin as a standard antioxidant, was measured at 560 nm against an appropriate blank. Superoxide radical scavenging activity was reported as the amounts that inhibited the superoxide anion radicals was achieved by %inhibition was estimated as follows:

$$\%\text{inhibition} = \frac{Abs_{control} - (Abs_{sample} - Abs_{blank}) \times 100}{Abs_{control}}$$

$Abs_{control}$ is the absorbance of 30 µL PBS mixed with 30 µL each of riboflavin, methionine, EDTA, and NBT was illuminated

Abs_{sample} is the absorbance of 30 µL extract mixed with 30 µL each of riboflavin, methionine, EDTA, and NBT was illuminated

Abs_{blank} is the absorbance of 30 µL extract mixed with 30 µL each of riboflavin, methionine, EDTA, and NBT was not illuminated

3.3.3.5 Oxygen radical antioxidant capacity (ORAC)

Oxygen radical antioxidant capacity was conducted to evaluate the free radical scavenging potential of the extract via a hydrogen atom transfer-based mechanism. The previously described method was modified to assess the antioxidant activity of the extracts against peroxyl radicals generated during thermal homolysis

of 2,2′-Azobis (2-amidinopropane) dihydrochloride (AAPH). The working solutions were made in 75 mM phosphate buffer (pH 7.4) by mixing 0.4 nM fluorescein (150 µL), 153 mM AAPH (25 µL), and 25 µL of either the extracts at a concentration of 1.0-0.002 mg/mL (2-fold dilution) or a reference antioxidant (Trolox). The reaction was carried out in a blank round bottom 96-well microplate by incubating the plant extract or the reference compound with the fluorescein solution at 37°C for 15 minutes. An aliquot of 25 µL of AAPH solution was added to the solution and the fluorescence intensity was immediately measured at an emission wavelength of 538 nm and an excitation wavelength of 485 nm every 5 minutes for 90 minutes. The antioxidant capacity was established based on Trolox equivalents per µM of TE/µg of the extract (Quek et al., 2021; Wetchakul et al., 2019). The computation using the following steps:

(1) Calculating the area under the curve

$$AUC_{Antioxidant} = \left(1/2 \times \left(\frac{R_1}{R_1}\right) + \left(\frac{R_2}{R_1}\right) + \left(\frac{R_3}{R_1}\right) + \ldots \left(\frac{R_n}{R_1}\right)\right) \times \text{time cycle}$$

By AUC = The area of area under the curve

R_1 = The initial fluorescence value

R_n = The fluorescence value in minutes n

Time cycle = The time to measure the repeated fluorescence (min)

(2) Calculate the Net AUC = $AUC_{Antioxidant} - AUC_{blank}$ the obtained value is plotted on a linear graph with the antioxidant concentration

The x-axis represents the Net AUC

The y-axis represents the antioxidant concentration

(3) Calculate the ORAC value (µM TE/ mg extract) and put it into the linear equation for the ubiquitous antioxidant Trolox. Determine the Trolox concentration in micromolar units and divide it by milligrams of extract.

3.3.4 Analysis of the Association Between Antioxidant Activity

The collection of 21 medicinal plants approved by the FDA and tested for antioxidant activity using the MCA, DPH, ABTS, FRAP, and NBT assays was used to analyze the correlation between the antioxidant activity of medicinal plants.

http://colab.reseaarch.google.com generated the heatmap for this analysis (accessed on 19 September 2023). Using a color scale with red indicating lower values and green indicating greater values, the antioxidant capacity is shown.

3.4 Evaluation of *in vitro* Antioxidant Capacities of Chosen Medicinal Plants

The *in vitro* antioxidant properties were examined again to verify the antioxidant efficiency by determining the 50% antioxidant inhibition value by MCA, DPPH, ABTS, and NBT assays. This was done after analyzing the correlation of antioxidant activity of the 21 medicinal plants to establish which medicinal plants possessed the highest percentage of inhibition.

3.5 Preliminary Profiling of the Chemical Constituents

The measured amount of active compounds found in medicinal plants and the active compounds found in medicinal plants were found using high-pressure liquid chromatography (HPLC) and liquid chromatography-mass spectrometer (LC-MS), respectively, for the analysis of active compounds found in plant extracts. The evaluation process will be transmitted to the Science and Technology Instruments Center (STIC), Mae Fah Luang University for examination. To prepare the medicinal plant extracts for LC-MS and HPLC fractionation, 1 mg of the extract was weighed, dissolved in 1 mL of 95% ethanol, and allowed to mix overnight at room temperature. The mixture was then filtered through with a syringe filter of 0.22 µm.

3.5.1 LC-MS Analysis

The qualitative chemical composition of the promising extract was analyzed with an Agilent 1290 Infinity-high-performance liquid chromatography system-tandem mass spectrometry method with electrospray ionization. The optimization of the instrument settings was as follows: the gas temperature was 325°C at a flow rate of 13 L/minutes, nitrogen was used as the nebulizer at 35 psi, and the capillary voltage was 3.5 kV. The mobile phase consisted of a linear gradient of 0.1% (v/v)

acetic acid in ultrapure water (A) and acetonitrile (B): 0 to 5.0 minutes, 5% B (v/v); 5.0 to 38.0 minutes, 42% B (v/v); 38.0 to 45 minutes, 5% B (v/v). The flow rate was 0.2 mL/minute and the injected volume was 5 µL. Putative compounds were processed using Agilent Mass Hunter Workstation software (Version B.04.00), Agilent MSC software (Version B.07.00), and the online METLIN database. The accuracy error threshold was set at ≤5 ppm (Wetchakul et al., 2019).

3.5.2 HPLC Analysis

The qualitative chemical composition of the promising extract was analyzed with a WATERS/ACQUITY Arc System (Shanghai, China) high-performance liquid chromatography system -tandem mass spectrometry method with electrospray ionization. Empower 3 software was used for peak integration. Chromatographic separation was achieved on a C18 column (Kinetex 5µm EVO C18 100A 150*2.1 mm). The mobile phase comprised 90% water-10% ACT (Acetonitrile) with isocratic elution for 18 minutes. The Diode array detector was kept at 425 nm. The rate of flow was 0.25 mL/min and the injection volume were 1.00 µL. The column temperature was kept at 30°C during chromatographic operation.

3.6 Encapsulation Procedures

The standardized *Curcuma longa* extract was chosen for further studies due to its promising *in vitro* antioxidant capacities. It has been well-described that there are three major chemical constituents responsible for the biological activities of *Curcuma longa* extract including curcumin (diferuloylmethane; approximately 70% of the curcuminoids), DMC (approximately 17% of the curcuminoids), and Bis-DMC (approximately 3% of the curcuminoids) (Amalraj et al., 2017; Huang et al., 2020; Sandur et al., 2007). Due to the hydrophobic character of curcumin, the compound has low oral bioavailability due to its poor water solubility, poor absorption from the digestive tract, and rapid metabolism (Amalraj et al., 2017; Huang et al., 2020; Sandur et al., 2007). To overcome this inconvenience, the microencapsulation technique has been used to improve the stability, solubility, and bioavailability of the extract.

3.6.1 Characterization of Microencapsulated Powders

The wall materials applied for encapsulation in this study were maltodextrin (MD with dextrose equivalence (D.E.) of 10-12; Vicchi Enterprise Co., Ltd. DE) and the combination of MD gum Arabic (GA; Sigma-Aldrich Chemie GmbH Steinheim, Germany) in an 8:2 and 6;4 (w/w) ratio. The standardized *Curcuma longa* extract at the concentration of 10 mg/mL dissolved in 95% ethanol was mixed with each wall material at a volume ratio of 1:1 to obtain core per wall weight ratios of 1:10 and 1:20 and continuously stirred at 100 rpm for 12 hours. The resulting mixture was subsequently spray-dried using a lab-scale spray dryer with a two-fluid nozzle (Minor-mode E, Niro A/S, China) with a feed flow rate using a nozzle diameter of 1.0 mm at 10 mL/minutes. The samples were run at the inlet air temperatures of 140±1°C, an exhaust temperature of 80±2°C, and a compressor air pressure of 1-31 bar. The obtained powders were harvested by a high-efficiency cyclone in a glass container and stored in a sealed sterile vial in desiccators at ambient temperature until further analysis. The encapsulation yield expressed as a percentage of mass (% w/w) was determined by dividing the weight of the obtained microcapsule powder by the total weight of the primary solid matter (Vonghirundecha et al, 2022).

3.6.1.1 The color parameters

The microcapsule color parameters were performed using the L^* (lightness) a^* (+; redness to -; greenness) b^* (+; yellowness to -; blueness) instrumental on a color analyzer (MiniScan X.E. Additionally, Model 45/0S, Hunter Associates Laboratory Inc., USA) with standard illuminant D65 with an area view of 19.812 mm and an observer angle of 10°C.

3.6.1.2 The morphology of microencapsulated

The morphology of the microencapsules powder will be transmitted to the Science and Technology Instruments Center (STIC), Mae Fah Luang University for examination using scanning electronic microscopy (SEM; SEMJSM5800LV model, Japan) at a magnification of 5000×.

3.6.1.3 Physicochemical characters

The physicochemical properties including bulk density, tapped density, flowability, cohesiveness, moisture content, water activity, hygroscopicity, and

water solubility index of the powders obtained from microencapsulated standardized *Curcuma longa* extract were assessed using the published procedures (Bednarska & Janiszewska-Turak, 2019; Janiszewska-Turak et al., 2017; Kang et al., 2019; Martins et al., 2022; Vonghirundecha et al, 2022).

The established protocols were followed for bulk and tapped densities. The flowability and cohesiveness of the microcapsule samples were further calculated to their bulk and tapped densities and expressed as Carr's index (CI) and Hausner ratio (H.R.), respectively.

The moisture content of the microencapsules powder (1 g) was reported as their weight loss percentage (%) after oven-drying at 105°C for 4 hours until a constant weight was achieved. Their water activities were measured by water activity meters (Aqua Lab, Series 3 C.E., USA). The solubility of the resulting microencapsules was analyzed by dissolving 1 g of the powder in 12 mL distilled water in a laboratory water bath at 30°C for 30 minutes and then centrifugation at 1000×g for 15 minutes. The supernatant was collected and oven-dried at 105°C for 12 hours.

3.6.1.4 The water solubility

The water solubility index (WSI) was expressed as a percentage. The hygroscopicity of the sample was determined by placing the powder samples (300 mg) in a desiccator filled with a saturated NaCl solution for 1 week at 25°C (75.29% R.H.; aw = 0.75), and then the weight of the storage samples was recorded. The hygroscopicity was presented in grams of adsorbed moisture per 100 grams of the original sample (g/100 g).

After oven-drying at 105°C for 4 hours until a constant weight was attained, the moisture content of the microcapsule powder (1 g) was recorded as a weight loss percentage (%). A water activity meter was used to track their water activities (Aqua Lab, Series 3 C.E., USA). The solubility of the resultant microcapsules was determined by dissolving 1 g of the powder in 12 mL of distilled water in a laboratory water bath at 30°C for 30 minutes, followed by centrifugation at 1000 g for 15 minutes. The supernatant was collected and oven-dried for 12 hours at 105°C. WSI was given in percentage form. The hygroscopicity of the microcapsule powder was tested by storing the powder samples (300 mg) in a

desiccator contained with a saturated NaCl solution for 1 week at 25°C (75.29% R.H.; aw = 0.75) and then recording the weight of the storage samples. The hygroscopicity was expressed in grams of adsorbed moisture per 100 grams of the original sample (g/100 g).

3.6.2 Functional Properties

The *in vitro* antioxidant properties and active chemical markers of the encapsulation powders were measured to confirm their biological functions.

The above-described protocols including MCA, DPPH, ABTS, FRAP, NBT, and ORAC assay were employed to estimate the antioxidant capacity of the microcapsule samples. In addition to the antioxidant properties, the TPC, TFC, and HPLC for quantifying the contents of curcumin, DMC, and Bis-DMC were used to describe the active constituents of selected microcapsule powder.

3.7 Neuroprotective Mechanisms of Microcapsules Containing Standardized *Curcuma longa* Extract

A well-established invertebrate model, *C. elegans* was employed to evaluate the toxicity and neuroprotective mechanisms of the chosen microcapsule (sCL11064).

On a daily basis, *C. elegans* (N2) was cultivated in nematode growth medium (NGM) plates supplemented with *Escherichia coli* (*E. coli*) OP50 as a food source. *C. elegans* was cultivated in S Medium with concentrated *E. coli* OP50 for tests that required liquid cultures (Ruangchuay et al., 2021; Wetchakul et al., 2019). Unless otherwise specified, all experiments were performed at 20°C. Age-synchronized *C. elegans* cultures were prepared using the alkaline hypochlorite technique.

3.7.1 Evaluations of Curcumin Microencapsulation Toxicity Testing in *C. elegans*

Toxicity experiments in *C. elegans* provide data from such a complete animal and have repeatedly been proven to be as predictive of rat LD_{50} ranking as mouse LD_{50} ranking (Hunt, 2016). Age-synchronous populations of L1 or L4 larvae were treated with the sCL11064 solution at varying concentrations (2-fold dilution)

ranking from 100-1,000 µg/mL for 48 hours in 96-well plates containing sterile K medium (50 mM NaCl and 30 mM KCL, pH 5.5) and *E. coli* OP50 at 20°C. The toxicity indicators, including feeding behavior by food clearance and pharyngeal pumping assay of the nematodes were recorded (Jiang et al., 2017; Lanzerstorfer et al., 2020; Ruangchuay et al., 2021).

3.7.1.1 Food clearance assay

The L1 stage *C. elegans* obtained from the synchronized S medium buffer (10 µL) was mixed into a 96-well plate containing 80 µL of *E. coli* OP50 (OD_{570} nm = 0.6) and 10 µL of the extracts at concentrations of 100, 250, 500, and 1,000 µg/mL. The cultures were then incubated at 20°C. The absorbance at 570 nm was measured every day for 7 days.

3.7.1.2 Pharyngeal pumping assay

The L4 stage *C. elegans* obtained from synchronization in S Medium buffer, volume 10 µL, was mixed into a 96-well plate containing *E. coli* OP50 (OD_{570} nm = 0.6) and sCL11064 at concentrations of 100, 250, 500, and 1,000 µg/mL and then incubated at 20°C. After 24 hours, the feeding rate of each *C. elegans* group was randomly counted by observing the contraction and relaxation of the pharyngeal muscles of *C. elegans* under a microscope for 1 minute, repeating 3 times. The results were reported in the form of the feeding rate of *C. elegans* per minute.

3.7.2 Evaluations of the Survival Rate in the Situation of Oxidative Stress in *C. elegans*

Paraquat was used to generate oxidative stress in worms. The synchronized L1 nematodes were transferred into seeded plates containing fresh S medium supplemented with *E. coli* OP50 and the sCL11064 solution (100, 250, 500, and 1000 µg/mL) for 24 hours.

The nematodes were then relocated to 96-well plates (approximately 20 worms/well) which contained fresh S medium supplemented with *E. coli* OP50, the sCL11064 solution, and 50 mM/L paraquat. Their mortalities were tracked every 12 hours till death based on their movement and form. The test was run three times with three duplicates each. As controls, nematodes subjected to paraquat without pretreatment with the extract and untreated worms were employed.

3.7.3 The Examination of the Neuroprotective Effects in Transgenic *C. elegans* Models

3.7.3.1 Dopaminergic Neurodegeneration Assay

Transgenic *C. elegans* BZ555 strain was employed to observe the protective effect of the sCL11064 on the progression of PD. The DAT-1 gene is expressed selectively in dopaminergic neurons and is involved in the transfer of dopamine between neuronal cells. This transgenic strain, in which GFP fluorophores are attached to the dopamine transporter DAT-1 on the dopaminergic neurons expresses human α-synuclein attached with a yellow fluorescence protein (YFP). Briefly, 6-OHDA was used to induce dopamine neuronal degeneration in the presence of the sCL11064 solution. After treatment at 20°C for 48 hours, the washed worms were mounted onto a 2% agar pad on a glass slide using 20 mM sodium azide and enclosed with a coverslip. Imaging of immobilized animals was taken with an IX51 inverted fluorescence microscope (Olympus, Tokyo, Japan) and its fluorescence intensity was performed by using ImageJ software (de Guzman et al., 2022; Fu et al., 2014; Nass et al., 2002).

3.8 Utilization of the Curcumin Microencapsules as a Functional Ingredient

3.8.1 The Preparation of the Extruded Snack

The sCL11064 food application feasibility test will be used as a functional ingredient in extruded snack form utilizing the extrusion technique, Figure 3.2 shows the production flow diagrams. The specific flour containing 10% w/w of the sCL11064 solution was prepared. A pilot scale single-screw extruder was selected to test the feasibility of the sCL11064 solution as a functional ingredient in an extruded snack. The extruder with a barrel of 19 mm diameter and 20:1 length-to-diameter ratio (L/D) consisting of two independent temperature zones controlled by electrical heating and compressed air cooling and a third zone also electrically heated was used. The condition in the extrusion experiments was set as the feed rate of 20

kg/hour and the screw compression ratio of 1:1, a die of 3 mm diameter, and a screw speed of 400 rpm. The processing temperature was kept constant at 40 to 155°C in the feeding and cooking zones, respectively. The temperature at the die end of the barrel which defined as was extrusion temperature was adjusted from 140 to 180°C (Rodríguez-Miranda et al., 2011). The extruded snacks were dried for 10 minutes in a forced-air oven at 80°C. The samples were collected, packed in vacuum-wrapped aluminum foil bags, and stored at 25°C until further use.

3.8.2 An analysis of the Nutritional Information

To determine the nutritional facts, bags of the extruded snacks were selected at random to be taken to the Institute of Food Research and Product Development at Kasetsart University (Bangkok, Thailand). The energy content per 100 g was determined using the following conversion factors: 4 kcal/g for carbohydrates, 4 kcal/g for protein, and 9 kcal/g for fat. This was done following the Thai FDA's guidelines and the Thai Recommended Daily Intake (RDI). Total energy, total carbohydrate, and energy from fat were among the analysis items that were carried out using, with minor adjustments, the International Officers and Committees 1993 with slight modifications (Chen & Gao, 1993; Lerttrakarnnon et al., 2021). With minor adjustments, other contents such as total fat, saturated fat, cholesterol, dietary fiber, sugar, sodium, vitamin B1 and B2, calcium, iron, and moisture were measured using the procedures outlined in the Official Methods of Analysis, the 21st Edition, AOAC International, Rockville, MD, USA (Lerttrakarnnon et al., 2021; Mongeau & Brassard, 1993). The amounts of ash and vitamin A per 100 g of samples were determined using previous procedures (Munzuroglu et al., 2003).

3.8.3 Sensory Evaluation

The sensory evaluation was conducted using the consumer technology analysis program provided by Zenme Co. Ltd (Thailand). One hundred individuals from four age groups (20-29, 30-39, 40-49, and >50 years) from various regions of Thailand participated in the test. More than 90% of the participants expressed interest in tasting and purchasing the extruded snack. Based on their food intake, exercise, drinking, and sleep patterns, the consumers were categorized into a group that practices regular and healthy behavior. Ten grams of the snack were placed in a pouch and sealed before testing.

The sensory panelists used a 9-point hedonic scale to score the extruded treats' appearance, odor, crispiness, taste, and likeability (1 = very disliked, 9 = very liked). Additionally, a 5-point hedonic scale was used to evaluate the product's acceptability, interest, and willingness to change (1 = like least, 5 = like most). The convenience and recommendations of consumers were also evaluated on a 7- and 10-scale, respectively.

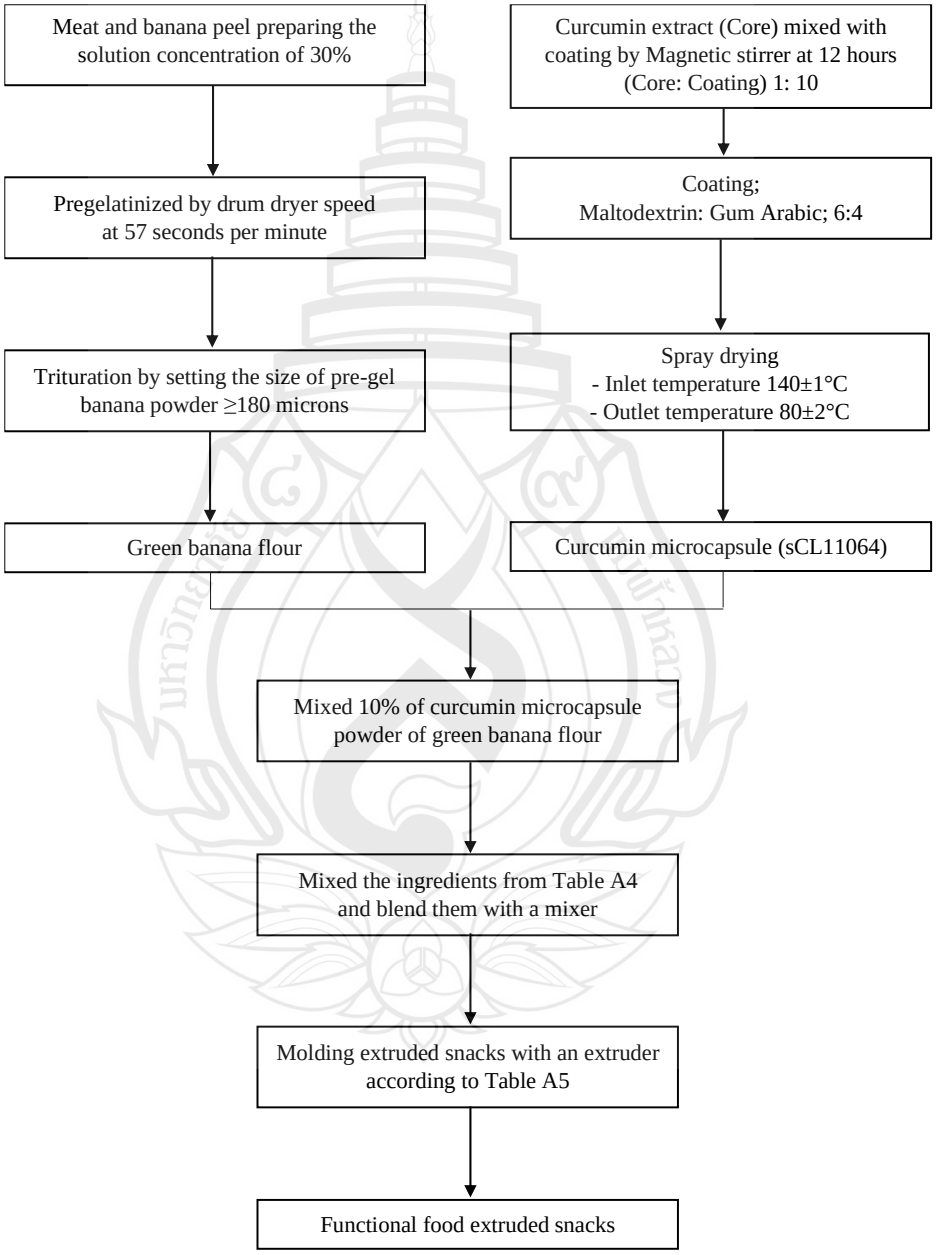


Figure 3.2 The flow diagrams of the production of extruded snacks green banana flour-based curcumin microencapsules

CHAPTER 4

RESULTS

4.1 Systematic Review of (Thai) Medicinal Plants with Neuroprotective Properties

4.1.1 Characteristics of the FDA-approved of Medicinal Plants

The feasibility and biological activities of the 211 FDA-approved dietary supplements derived from medicinal plants were preliminary screened using a systematic review process and represented in Figure 3.1. Of the medicinal plants the FDA has allowed for use in dietary supplements, 153 species are grown in Thailand, making up about 73% of the total, while the other 58 species are not found in Thailand (Figure 4.1A). Based on the list of FDA-approved dietary supplements derived from medicinal plants, the 153 plant species of medicinal plants found in Thailand can be divided into 64 families, the two most commonly found families are Asteraceae (n=12 species) and Rosaceae (n=12), followed by Lamiaceae (n=10), Fabaceae (n=10), Poaceae (n=7), and Rutaceae (n=6), respectively (Figure 4.1B).

4.1.2 Medicinal Plants with Potential Antioxidant Properties

The findings of a thorough review of the literature on 153 medicinal plants available in Thailand 116 species demonstrated to have primary antioxidant and neuroprotective properties by inhibiting AChE. The criteria for studies screening: the medicinal plants' IC_{50} free radical suppression DPPH free radical activity results must be reported and the part used has to match the FDA report. The study results show that two kinds of medicinal plants found in Thailand but have not previously been reported for their antioxidant properties are *Amorphophallus brevispathus* (Buk) in the rhizome and the petal of rose in *Rosa spp*. and hybrid.

Furthermore, data regarding the 20 medicinal plants' IC_{50} value for antioxidant activity was not found. The study suggests that FDA-approved medicinal plants are available in Thailand and can be used in dietary supplements were successful in scavenging free radical DPPH at levels of very strong 31.90% (n=37 species), strong

19.83% (n=23), moderate 10.34% (n=12), weak 5.17% (n=6). Most of the medicinal plants mentioned above were inactive up to 32.76% (n=38) (Figure 4.2A). While the antioxidant activity of $ABTS^{+}$ was at a very strong 39.66% (n=46), followed by not active 23.28% (n=27), strong 19.83% (n=23), weak 10.34% (n=12), and moderate 6.90% (n=8) in that order (Figure 4.2B). Antioxidant activity was split into five levels to analyze the IC_{50} value (µg/mL): <50; Very strong, 50-100; Strong, 101-250; Moderate, 250-500; Weak, and >500; Not active (Budaraga & Putra, 2021; Jumina et al., 2019; Kusumawati et al., 2021).

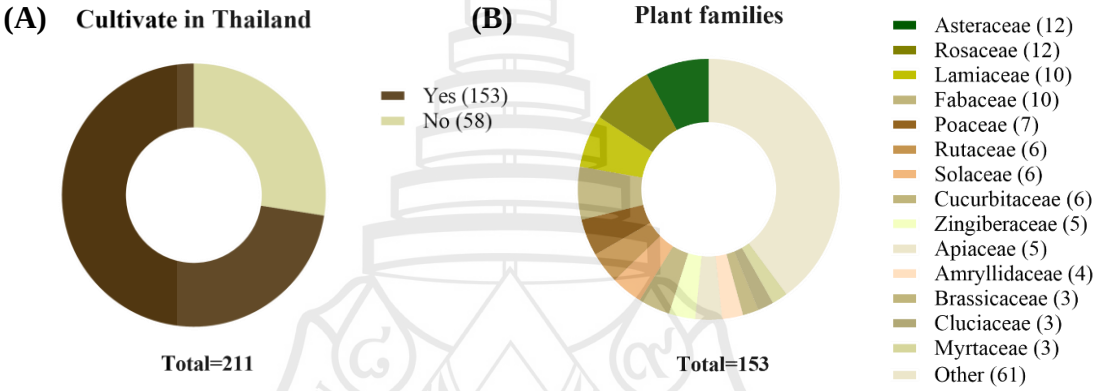


Figure 4.1 The list of Thai FDA-approved dietary supplements obtained from medicinal plants. (A) Medicinal plants cultivated in Thailand and (B) Number of plant families cultivated in Thailand

4.1.3 Correlation between Assays

Because the aim is to find correlations with Thai medicinal plants that are FDA-approved and that can be used as dietary supplements, that assess the primary antioxidant activity of these medicinal plants based on a systematic review of the antioxidant activity data. With 116 species, a significant strongly positive correlation ($r = 0.993$, $p<0.001$) between DPPH and ABTS is shown in Figure A1.

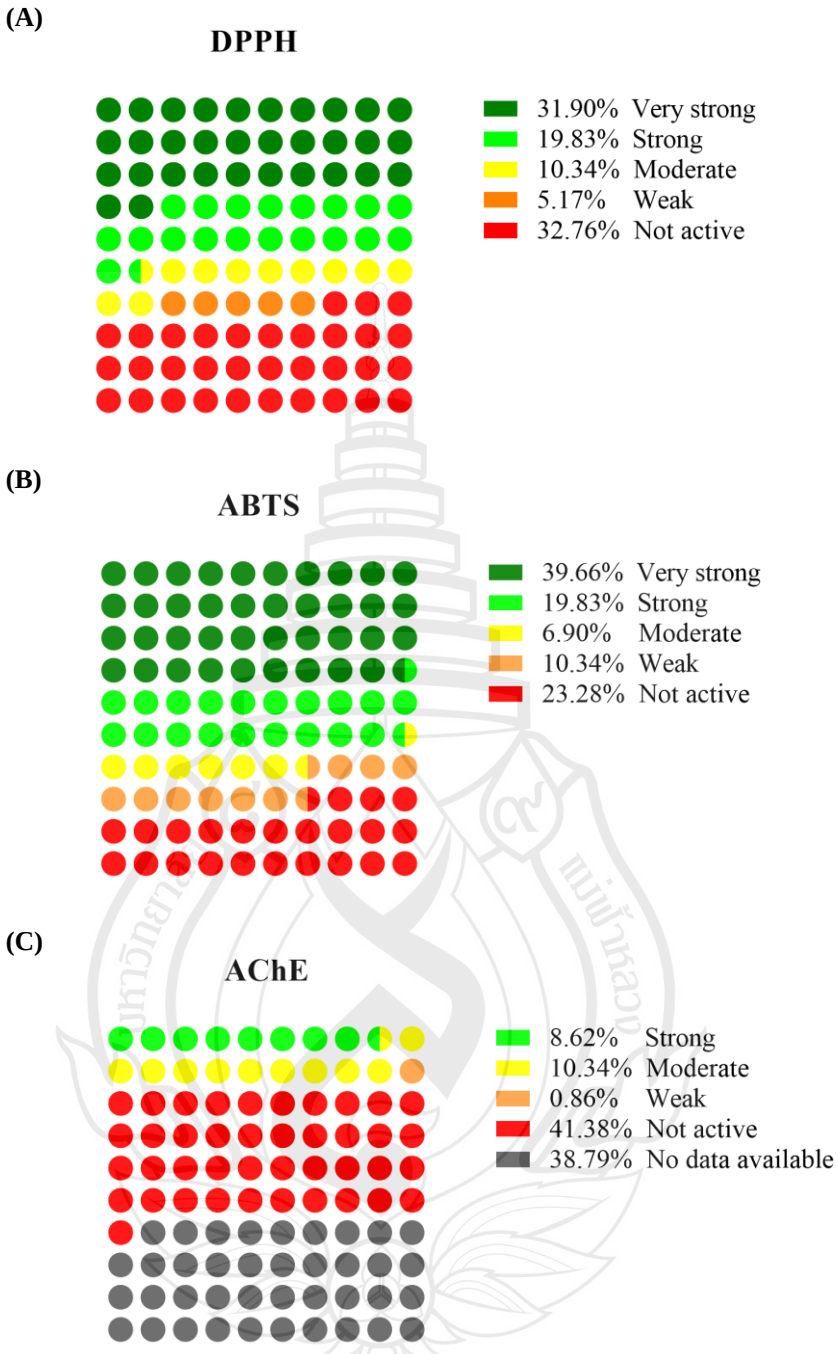


Figure 4.2 IC_{50} value of the antioxidant activity and neuroprotective effect analysis, using (A) DPPH method, (B) ABTS method, and (C) Acetylcholinesterase of plant-based antioxidants from the list of Thai FDA-approved dietary supplements derived from medicinal plants

4.1.4 Potential Acetylcholinesterase Inhibitory

Reports on the inhibitory effects of acetylcholinesterase will be conducted with the 116 Thai medicinal plants that the FDA approved for use as dietary supplements after screening them for antioxidant activity. The results of a systematic review of the literature, as shown in Figure 4.2C, suggest that certain medicinal plants that are available in Thailand and have FDA approval for use in dietary supplements have strong effects (8.26%), moderate effects (10.34%), weak effects (0.86%), and no AChE inhibitory activity (41.38%). On the other hand, information about the AChE inhibitory effects on the total number of medicinal plants which comprises more than 34 species, or 38.79% was unavailable. Therefore, a systematic review discovered that Thailand has access to FDA-approved medicinal plants that can be used for producing dietary supplements that have antioxidant and AChE inhibitory activities.

There are twenty-eight known medicinal plants at this time. However, to advance these medicinal plant extracts into the functional food category, they must be simple to employ economically. As seen in Table A2, 21 different varieties of medicinal plant extracts are readily available commercially, which is why we are utilizing them in the next phase of our investigation. Thus, to explore the potential for future development into functional food products, these extracts will be studied *in vitro* and at the *in vivo* level.

4.2 Evaluation of *in vitro* Antioxidant Capacities of Potential Standardized Crude Extracts (n=21)

4.2.1 Quantification Analysis of Chemical Markers for Antioxidant Activity

4.2.1.1 Total phenolic content (TPC)

The total phenolic content (TPC) was estimated spectrophotometrically using the Folin-Ciocalteu method, the TPC of the phenolic component was reported in milligrams of gallic acid equivalent per gram of extract, as shown in Table 4.1. The results found that TPC ranged from 165.02±8.25 to 1,378.19±85.34 mg of gallic acid equivalent/g of extract. *Coffea arabica* is the richest source of phenolics, followed by *Curcuma longa* and *Camellia sinensis* with statistical significance at $p<0.05$. These values are 1,378.19±85.34, 514.13±50.55, and 387.43±31.26 mg of gallic acid equivalent/g of extract, respectively.

4.2.1.2 Total flavonoid content (TFC)

The total flavonoid content (TFC) of different medicinal plant extracts was measured spectrophotometrically by using the aluminium chloride colorimetric assay. The TFC of 21 medicinal plants was analyzed, and the results were reported as mg of catechin equivalent per g of extract. The results found that TFC ranged from 1.65±0.16 to 521.47±10.16 mg of catechin equivalent/g of extract. *Coffea arabica*a had the highest flavonoid content, followed by *Curcuma longa* and *Bacopa monnieri* with statistical significance at $p<0.05$. These values are 521.47±10.16, 185.22±8.87, and 80.35±3.95 mg of catechin equivalent/g of extract, respectively, as shown in Table 4.1.

4.2.2 Metal Chelating Assay (MCA)

This study aims to determine the transition binding value percentage inhibition, by analyzing 21 FDA-approved medicinal plants for their ability to bind to transition metals that catalyze oxidation reactions. The results found that %inhibition range of 25.09±1.28 to 108.41±4.41, *Aloe vera* had the highest ability to bind to transition metals, followed by *Moringa oleifera* and *Matricaria chamomilla*, all of which had %inhibition values of 108.41±4.41, 107.80±9.80, and 104.26±9.12, respectively. These results were statistically significant at $p<0.05$. As shown in Table 4.2.

Table 4.1 The main active ingredients antioxidant activities of 21 medicinal plants

Medicinal plants	**Part used**	**Total content of**	
		Phenolic[1]	**Flavonoid**[2]
Allium sativum	Rhizome	242.52±17.14^{de}	70.22±11.79^{d}
Aloe vera	Gel	211.52±15.78^{defgh}	35.41±2.85^{gh}
Bacopa monnieri	Whole tree	258.02±12.80^{d}	80.35±3.95^{c}
Camellia sinensis	Fruit	387.43±31.26^{c}	15.79±1.10^{j}
Capsicum annuum	Leaf	180.14±10.55^{fgh}	36.36±2.51^{fg}
Carthamus tinctorius	Flower	222.37±11.09^{defg}	28.45±6.10^{ghi}
Centella asiatica	Leaves	210.75±21.78^{defgh}	1.65±0.16^{k}
Citrus x *aurantium*	Fruit	165.02±8.25^{h}	15.16±1.45^{j}
Coffea arabica	Seeds	1,378.19±85.34^{a}	521.47±10.16^{a}
Curcuma longa	Rhizome	514.13±50.55^{b}	185.22±8.87^{b}
Daucus carota	Root	215.78±17.45^{defgh}	34.15±3.95^{gh}
Ganoderma lucidum	Fruit	205.32±16.94^{defgh}	33.51±0.95^{gh}
Garcinia mangostana	Peel	241.74±16.82^{de}	11.95±1.11^{j}
Gynostemma pentaphyllum	Leaves	203.38±21.19^{defgh}	28.45±2.19^{ghi}
Kaempferia parviflora	Rhizome	200.28±10.65^{efgh}	27.82±1.64^{hi}
Matricaria chamomilla	Flower	169.67±13.87^{gh}	26.55±1.45^{ghij}
Moringa oleifera	Leaf	204.16±14.53^{defgh}	32.56±1.64^{gh}
Piper nigrum	Seed	230.51±5.07^{def}	20.22±1.90^{ij}
Tagetes erecta	Flower	173.94±8.16^{gh}	13.26±0.55^{j}
Terminalia chebula	Fruit	215.01±5.85^{defgh}	43.96±0.95^{f}
Zingiber officinale	Rhizome	218.49±17.14^{defgh}	51.87±3.84^{e}

Note [1,2]: Total phenolic content (TPC) and total flavonoid content (TFC) expressed as mg of gallic acid equivalence per g of extract and mg of catechin equivalence per g of extract

[a-k]: Values in the same row with different superscripts are significantly different ($p<0.05$)

4.2.3 Chain-breaking Antioxidant Capacities

4.2.3.1 DPPH radical scavenging activity

Assessment of the DPPH antioxidant capacity of extracts from 21 FDA-approved medicinal plants, with results expressed as a percentage of DPPH free radical inhibition, with the inhibition range of 3.35±0.24 to 113.19±6.95. Medicinal plant extracts with a high DPPH free radical inhibition were found *Tagetes erecta* exhibited the highest %inhibition values, followed by *Curcuma longa* and *Coffea arabica*, all of which had %inhibition value of 113.19±6.95, 108.36±2.35, and 90.72±0.34, respectively. These results were statistically significant at $p<0.05$. As shown in Table 4.2.

4.2.3.2 ABTS radical scavenging activity

Assessment of the ABTS antioxidant capacity of extracts from 21 FDA-approved medicinal plants, with results expressed as a percentage of ABTS free radical inhibition, with the inhibition range of 6.40±0.49 to 102.99±0.23. Medicinal plant extracts with a high ABTS free radical inhibition were found *Curcuma longa* exhibited the highest %inhibition values, followed by *Camellia sinensis* and *Coffea arabica*, all of which had a %inhibition value of 102.99±0.23, 100.30±0.07, and 90.63±0.41, respectively. These results were statistically significant at $p<0.05$. As shown in Table 4.2.

4.2.3.3 Ferric reducing antioxidant power (FRAP)

Examination of medicinal plant extracts' ability to reduce transition metal from a list of 21 FDA-approved medicinal plants. Ability values will be reduced as a result and reported. Transition metal expressed as micromoles of ferrous per mg of extract. The ability to reduce transition metals of medicinal plant extracts was found to be in the range of 0.91±0.49 to 138.88±7.13 µM $FeSO_4$/mg, *Coffea arabica* was found to have the highest ability to reduce transition metals, followed by *Curcuma longa* and *Bacopa monnieri*. This is a value of 138.88±7.13, 30.22±2.27, and 13.95±0.35 µM $FeSO_4$/mg, and it is statistically significant at $p<0.05$. As shown in Table 4.2.

4.2.3.4 Nitro blue tetrazolium assay (NBT)

Examination of the antioxidant activity of superoxide anion of medicinal plant extracts derived from the list of 21 FDA-selected plants using the Nitro blue tetrazolium assay. The results will be expressed as the superoxide anion inhibition

percentage of free radicals, with the inhibition range of 11.86±0.68 to 123.77±0.72. *Curcuma longa* was shown to have the best ability to superoxide anion free radicals, followed by *Coffea arabica* and *Terminalia chebula*. The values are 123.77±0.72, 98.36±0.96, and 95.20±1.05, with statistical significance at $p<0.05$. As shown in Table 4.2.

4.2.4 The Association between Antioxidant Activity

The results from the examination of medicinal plants' antioxidant capacity, were extracted from the list of 21 FDA-selected plants. The heatmap analysis, as shown in Figure 4.3, summarized all 21 medicinal plants and divided the amount of antioxidant efficiency from color to examine the correlation between medicinal plants' antioxidant activity in each of the five assays. Green gradually switches to red (low to high antioxidant activity), six varieties of medicinal plants: *Bacopa monnieri*, *Camellia sinensi*, *Coffea arabica*, *Curcuma longa*, *Tagetes eracta*, and *Terminalia chebula*, were found to have the most consistent antioxidant activity in medicinal plants. Each of the six varieties of medicinal plants will be studied in a further way.

Table 4.2 The antioxidant capacities of 21 medicinal plants

Medicinal plants	**Metal chelating**[1] **(%inhibition±SD)**	**DPPH**[2] **(%inhibition±SD)**	**ABTS**[3] **(%inhibition±SD)**	**FRAP**[4] **(μM $FeSO_4$/mg)**	**NBT**[5] **(%inhibition±SD)**
Allium sativum	90.50±6.98^{efg}	6.25±0.58^{l}	23.28±0.67^{h}	6.98±0.19^{d}	11.86±0.68^{n}
Aloe vera	108.41±4.41^{a}	11.69±0.44^{k}	11.05±0.52^{l}	7.13±0.70^{d}	32.46±1.40^{jk}
Bacopa monnieri	62.34±4.90^{h}	40.29±2.05^{e}	64.70±0.93^{d}	13.95±0.35^{c}	18.98±1.34^{m}
Camellia sinensis	25.09±1.28^{j}	90.64±0.04^{c}	100.30±0.07^{b}	13.37±0.22^{c}	80.12±4.79^{c}
Capsicum annuum	99.04±0.96^{bcde}	12.10±0.71^{k}	11.37±1.06^{l}	0.91±0.02^{f}	48.15±2.69^{g}
Carthamus tinctorius	95.60±4.60^{cde}	20.95±0.34^{hi}	19.65±0.48^{ij}	6.92±0.15^{de}	28.11±1.54^{l}
Centella asiatica	83.30±5.71^{fg}	16.31±0.41^{j}	14.74±0.62^{k}	7.81±0.15^{d}	37.88±2.37^{jk}
Citrus x *aurantium*	92.93±4.83^{de}	16.92±1.14^{j}	27.92±0.99^{f}	6.24±0.65^{de}	53.87±3.74^{f}
Coffea arabica	66.99±6.23^{h}	90.72±0.34^{c}	99.63±0.41^{b}	138.88±7.13^{a}	98.36±0.96^{b}
Curcuma longa	38.26±2.49^{i}	108.36±2.35^{b}	102.99±0.23^{a}	30.22±2.27^{b}	123.77±0.72^{a}
Daucus carota	82.03±1.72^{g}	24.18±0.38^{g}	17.43±1.19^{j}	8.82±0.17^{d}	35.84±2.75^{k}
Ganoderma lucidum	99.76±1.04^{abcde}	4.79±0.21^{l}	10.98±1.06^{l}	6.82±0.06^{de}	40.64±1.65^{ij}
Garcinia mangostana	83.24±7.66^{fg}	30.80±1.45^{f}	69.18±3.91^{c}	8.25±0.58^{d}	59.45±5.39^{e}
Gynostemma pentaphyllum	97.83±1.63^{cde}	3.35±0.24^{l}	20.59±1.26^{i}	6.77±0.02^{de}	42.50±2.16^{hi}
Kaempferia parviflora	96.88±0.22^{cde}	5.52±0.28^{l}	6.40±0.49^{m}	1.44±0.11^{f}	47.85±1.93^{g}
Matricaria chamomilla	104.26±9.12^{abc}	18.31±1.09^{ij}	24.71±2.13^{gh}	3.90±0.19^{ef}	45.77±1.66^{gh}
Moringa oleifera	107.80±9.80^{ab}	12.31±0.38^{k}	18.73±0.91^{ij}	2.06±0.08^{f}	38.36±1.94^{jk}

Table 4.2 (continued)

Medicinal plants	**Metal chelating**[1] (%inhibition±SD)	**DPPH**[2] (%inhibition±SD)	**ABTS**[3] (%inhibition±SD)	**FRAP**[4] (μM $FeSO_4$/mg)	**NBT**[5] (%inhibition±SD)
Piper nigrum	92.16±3.01^{ef}	20.61±1.09^{hi}	27.10±1.07^{fg}	1.62±0.05^{f}	75.31±0.74^{d}
Tagetes erecta	102.23±4.98^{abcd}	113.19±6.95^{a}	42.23±3.50^{e}	2.48±0.11^{f}	19.74±0.38^{m}
Terminalia chebula	65.39±4.34^{h}	78.52±2.15^{d}	99.55±0.08^{b}	8.02±0.17^{d}	95.20±1.05^{b}
Zingiber officinale	90.50±2.98^{efg}	22.49±0.96^{gh}	23.15±1.73^{h}	1.62±0.10^{f}	24.34±1.69^{l}

Note [1]: Preventive properties metal chelating activity (MCA) of extracts were expressed percentage chelating capacity (%inhibition), [2,3]: Free radical scavenging activities of extracts were expressed interns of their inhibitory activity against DPPH and ABTS+ radicals (%inhibition), and [4,5]: Single electron transfer of the ferric reducing antioxidant power (FRAP) and superoxide anion radical by the nitroblue tetrazolium (NBT) were expressed as micromoles of ferrous per mg of extract and inhibitory activity, respectively

[a-n]: Values in the same row with different superscripts are significantly different ($p<0.05$)

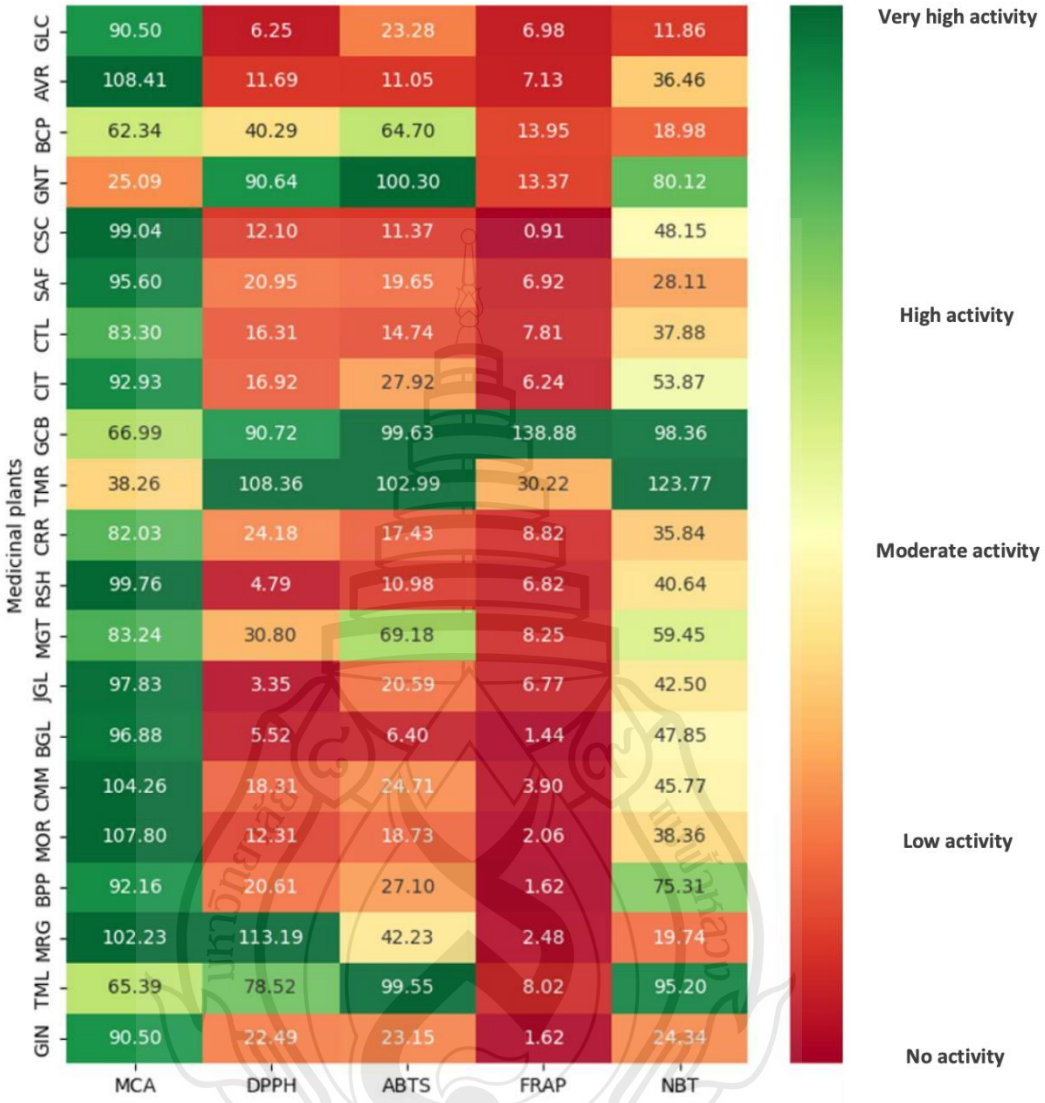


Figure 4.3 Heatmap analysis of antioxidant capacities of medicinal plants (n=21). The values in the heatmap reflect the percentage of free radical scavenging for each extract, evaluated through DPPH, ABTS, and NBT assays, along with their antioxidant capacity as shown by the FRAP values. It also includes the percentage of metal chelating inhibition evaluated using the MCA assay. The tested extracts include: GLC; *Allium sativum*, AVR; *Aloe vera*, BCP; *Bacopa monnieri*, GNT; *Camellia sinensis*, CSC; *Capsicum annuum*, SAF; *Carthamus tinctorius*, CTL; *Centella asiatica*, CIT; *Citrus* x *aurantium*, GCB; *Coffea arabica*, TMR; *Curcuma longa*, CRR; *Daucus carota*, RSH; *Ganoderma lucidum*, MGT; *Garcinia mangostana*, JGL;

Gynostemma pentaphyllum, BGL; *Kaempferia parviflora*, CMM; *Matricaria chamomilla*, MOR; *Moringa oleifera*, BPP; *Piper nigrum*, MRG; *Tagetes erecta*, TML; *Terminalia chebula*, and GIN; *Zingiber officinale*.

4.3 Evaluation of *in vitro* Antioxidant Capacities of Chosen Standardized Crude Extracts (n=6)

4.3.1 Metal Chelating Assay (MCA)

An examination of 6 medicinal plants' ability of the extracts to bind transition metals that catalyze oxidation, will be expressed as the amounts that inhibited the ferrous ion ferrozine complex by 50% (IC_{50}). The results found that *Curcuma longa* had the highest ability to bind to transition metals, followed by *Bacopa monnieri* and *Terminalia chebula*, with IC_{50} values of 0.06±0.00, 0.21±0.01, and 0.41±0.01 mg/mL, respectively. These results were statistically significant at $p<0.05$. As shown in Table 4.3.

4.3.2 Chain-breaking Antioxidant Capacities

4.3.2.1 DPPH radical scavenging activity

Assessment of the DPPH antioxidant capacity of extracts from 6 medicinal plants, with results expressed as a DPPH free radical inhibition value of 50% (IC_{50}). Medicinal plant extracts have been found to have the capacity to inhibit free radicals. *Coffea arabica* exhibited the highest free DPPH, followed by *Bacopa monnieri* and *Curcuma longa*, with IC_{50} values of 0.17±0.00, 0.28±0.10, and 0.42±0.02 mg/mL, respectively. These results were statistically significant at $p<0.05$. As shown in Table 4.3.

4.3.2.2 ABTS radical scavenging activity

Assessment of the ABTS antioxidant capacity of extracts from 6 medicinal plants, with results expressed as an ABTS free radical inhibition value of 50% (IC_{50}). Medicinal plant extracts have been found to have the capacity to inhibit free radicals. *Coffea arabica* exhibited the highest free ABTS, followed by *Curcuma longa* and *Bacopa monnieri*, with IC_{50} values of 0.12±0.01, 0.18±0.01, and 2.82±0.29 mg/mL, respectively. These results were statistically significant at $p<0.05$. As shown in Table 4.3.

4.3.2.3 Nitro blue tetrazolium assay (NBT)

Examination of the antioxidant activity of superoxide anion of medicinal plant extracts derived from 6 medicinal plants using the nitro blue tetrazolium assay.

The results will be expressed as the concentration that caused 50% inhibition (IC_{50}) of superoxide anion radicals. *Tagetes eracta* was shown to have the highest ability to inhibit superoxide anions, followed by *Camellia sinensis* and *Terminalia chebula*, with IC_{50} values of 0.06±0.01, 0.06±0.02, and 0.13±0.06 mg/mL, respectively. These results were statistically significant at $p<0.05$. As shown in Table 4.3.

After six different medicinal plants were examined for antioxidant activity, it was discovered that *Curcuma longa* possessed a substantial amount of phenolic and flavonoid contents and demonstrated strong antioxidant properties once evaluated with MCA, DPPH, ABTS, FRAP, and NBT. For these reasons, *Curcuma longa* was chosen to be transformed into microencapsules in the next experiments.

Table 4.3 The antioxidant capacities of 6 medical plants

Medicinal plants	**Metal chelating[1] (IC_{50}; mg/mL)**	**DPPH[2] (IC_{50}; mg/mL)**	**ABTS[3] (IC_{50}; mg/mL)**	**NBT[4] (IC_{50}; mg/mL)**
Bacopa monnieri	0.21±0.01^{a}	0.38±0.10^{a}	2.82±0.29^{b}	0.21±0.10^{bc}
Camellia sinensis	1.23±0.31^{a}	0.55±0.03^{a}	2.97±0.24^{b}	0.06±0.02^{a}
Coffea arabica	1.19±0.19^{a}	0.17±0.00^{a}	0.12±0.01^{a}	0.29±0.13^{cd}
Curcuma longa	0.06±0.00^{a}	0.42±0.02^{a}	0.18±0.01^{a}	0.38±0.07^{d}
Tagetes erecta	0.91±0.07^{a}	12.40±3.03^{b}	8.73±1.00^{d}	0.06±0.01^{a}
Terminalia chebula	0.41±0.01^{a}	0.98±0.03^{a}	6.43±0.13^{c}	0.13±0.06^{ab}

Note [1]: Preventive properties metal chelating activity (MCA) of extracts were expressed as the amounts that inhibited the ferrous ion ferrozine complex by 50% (IC_{50}; mg/mL), [2,3]: Free radical scavenging activities of extracts were expressed as the concentration caused 50% inhibition of DPPH and ABTS+ radicals (IC_{50}; mg/mL), and [4]: Single electron transfer of the superoxide anion radical by the nitroblue tetrazolium (NBT) were expressed as the concentration that caused 50% inhibition of superoxide anion radicals (IC_{50}; mg/mL)

[a-d]: Values in the same row with different superscripts are significantly different ($p<0.05$)

4.4 Determination of Bioactive Compounds of *Curcuma longa*

LC-MS analysis of the *Curcuma longa* from ethanol extract was used to identify the biocomponents of the *Curcuma longa* extract with antioxidant activity. Three curcuminoids were identified in the *Curcuma longa* extract: curcumin, DMC, and Bis-DMC (Table 4.4). Each of the curcuminoids is separated effortlessly and does not co-elute. Figure 4.4 provides all the chemical characteristics of the compounds that were found.

In addition, the three curcuminoids were also quantified HPLC. As shown in Table 4.5, the curcuminoid components in *Curcuma longa* extract were found to include 69.83±2.00 mg/kg of curcumin, 10.28±0.28 mg/kg of DMC, and 4.22±0.09 mg/kg of Bis-DMC, respectively.

Table 4.4 Chemical characteristics of identified compounds from *Curcuma longa* by LC-MS

Compounds	**Retention Time (min)**	**Molecular Formula**	**Molecular mass**	**Match score**
Curcumin	19.84	$C_{21}H_{20}O_6$	368.12	97.40
DMC	19.68	$C_{20}H_{18}O_5$	338.12	98.27
Bis-DMC	19.45	$C_{19}H_{16}O_4$	308.11	98.27

Note DMC; Demethoxycurcumin, Bis-DMC; Bisdemethoxycurcumin

Table 4.5 HPLC conditions and contents of chemical markers found in *Curcuma longa* extract

Parameters	**Curcumin**	**DMC**	**Bis-DMC**
Retention time (min)	12.75±0.01	11.80±0.00	10.92±0.01
Peak area	1174692.67±34002.63	220591.67±6626.25	55750.33±1679.29
%Area	80.96±0.03	15.20±0.03	3.84±0.01
Height (AU)	45329.00±1234.70	9991.00±271.92	2656.33±69.02
Content (mg/kg)	69.83±2.00	10.08±0.28	4.22±0.09

Note DMC; Demethoxycurcumin, Bis-DMC; Bisdemethoxycurcumin

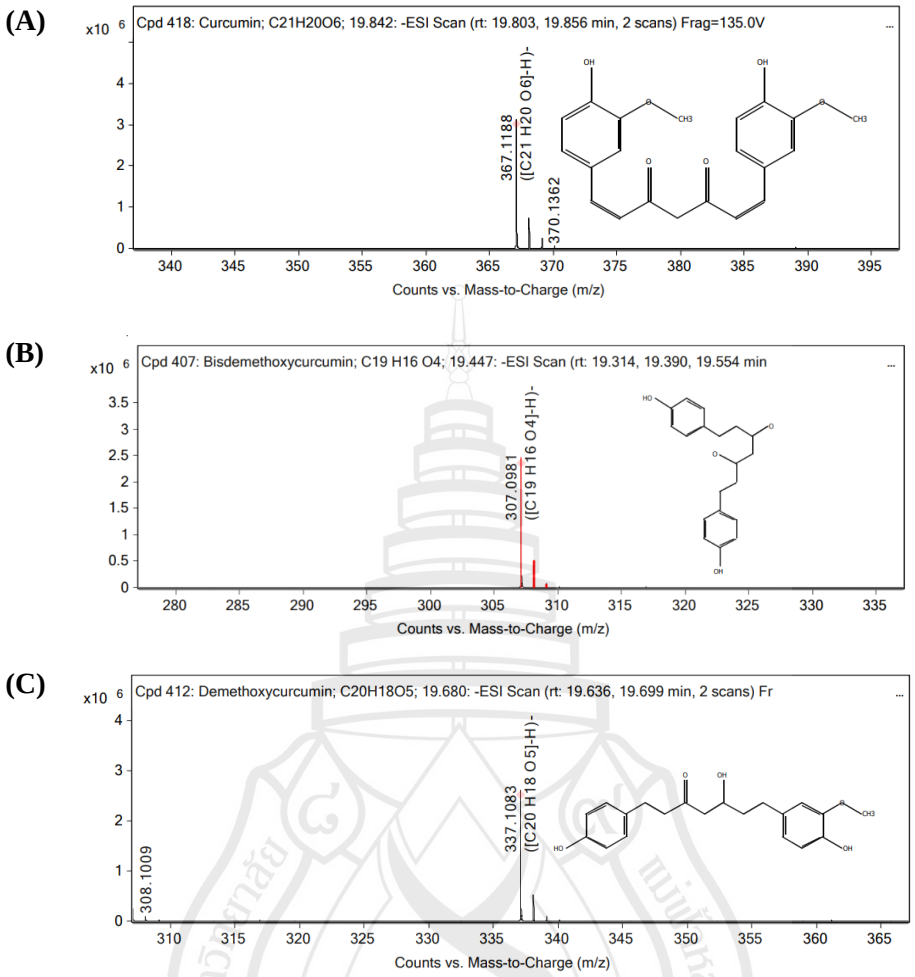


Figure 4.4 LC-MS Chromatogram of *Curcuma longa* extract, (A) Curcumin, (B) Demethoxycurcumin, and (C) Bisdemethoxycurcumin

After identifying the active ingredients in *Curcuma longa* extract, the extract will be transformed into smaller particles in microencapsules to preserve the plant's active ingredients and decrease the extract's water solubility limit for improved solubility.

4.5 Formation of Microencapsulation

4.5.1 Characterization of Microencapsules

4.5.1.1 Microencapsulated curcumin

Spray drying was used to produce *Curcuma longa* extract in microencapsulated form, Figure 4.5 shows the appearances of 6 curcumin microencapsules formulas: sCL12010, sCL12082, sCL12064, sCL11010, sCL11082, and sCL11064. As shown in Table 4.6, the six formulations varied in the proportion of extract-to-wall materials blended in the core-to-wall weight ratios of 1:10 and 1:20. As well as in the ratios of maltodextrin and gum Arabic employed for encapsulation, which were 10:0, 8:2, and 6:4. The encapsulation yields of curcumin microencapsules that were encapsulated using MD:GA ranged from 55.0 to 61.0%. The formulations showing a 1:20 core:wall materials ratio yielded higher yields than those with a 1:10 ratio (61.0% and 60.5%, respectively). The microencapsules with a wall ratio of 6:4 between MD:GA produced higher yields than those with other ratios, according to the yields.

4.5.1.2 The color attributes

The color values reflect the curcumin microencapsules brightness and saturation level (Table 4.6). All of the curcumin microencapsules showed high lightness with L^* values ranging from 72.32±0.00 to 79.43±0.08 and a^* values slightly above 0, indicating a modest tendency towards red color. In addition, all six curcumin microencapsules formulae had b^* values above 0, which showed a strong inclination toward yellow coloration due to the curcumin. Curcumin microencapsules formulated with extract-to-wall material mixed at a core-wall weight ratio of 1:10, that is sCL11064, sCL11082, and sCL11010, were found to have a significantly more yellow color than formulas with a ratio of 1:20, which were 89.25±0.08, 88.08±0.05, and 79.67±0.09, respectively.

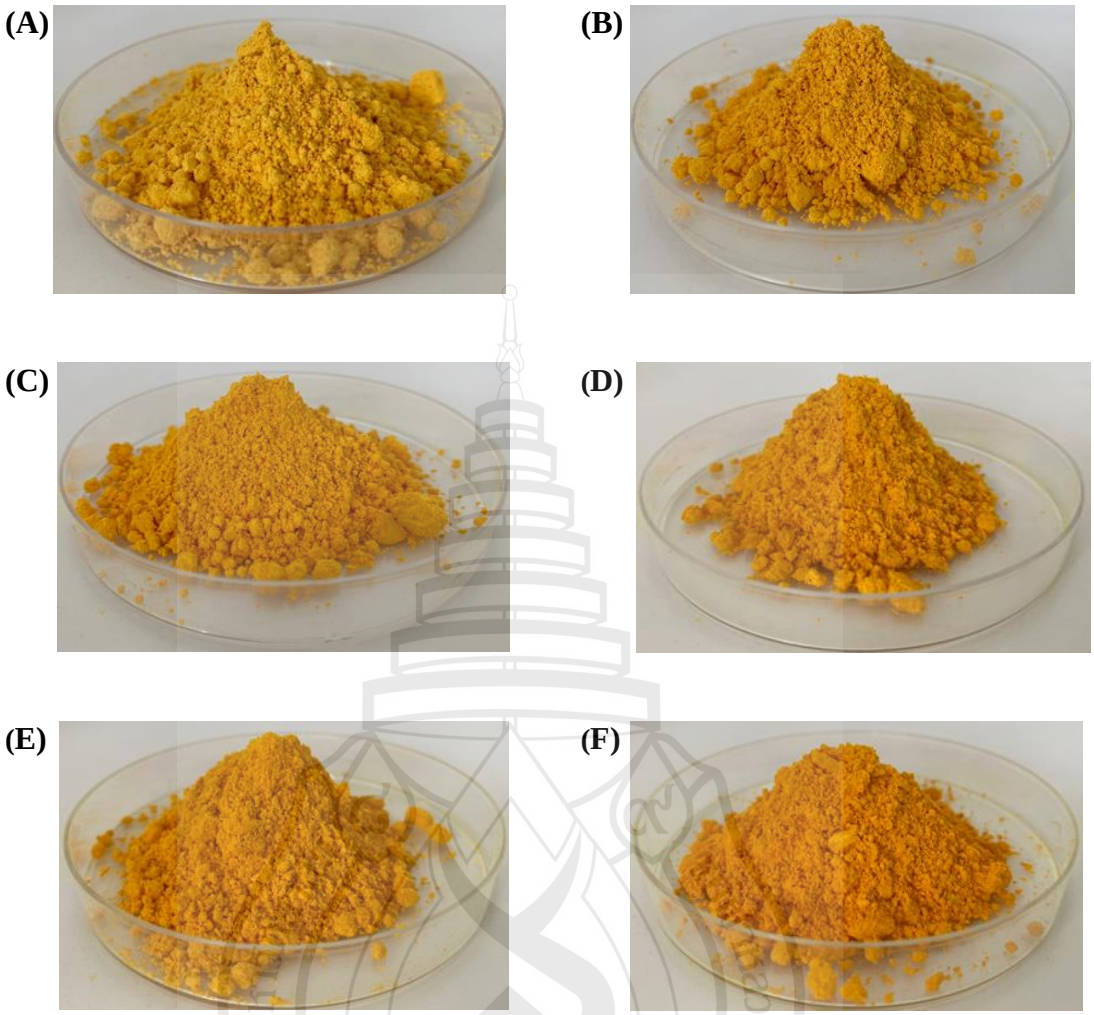


Figure 4.5 Appearance of curcumin microencapsules, (A) sCL12010, (B) sCL12082, (C) sCL12064, (D) sCL11010, (E) sCL11082, and (F) sCL11064

Table 4.6 Ratios of wall material, yields, and color parameters of curcumin microcapsules

Treatment code	Ratio of core: wall materials	Concentrate (Core:Coating)	Encapsulation yield (%)	Color parameter		
				L^*	a^*	b^*
sCL12010	1:20	MD:GA (10:0)	55.5	79.43±0.08[a]	10.18±0.06[f]	64.61±0.38[f]
sCL12082	1:20	MD:GA (8:2)	56.0	76.52±0.01[b]	16.57±0.01[e]	68.23±0.07[e]
sCL12064	1:20	MD:GA (6:4)	61.0	76.16±0.02[c]	17.39±0.02[d]	71.96±0.10[d]
sCL11010	1:10	MD:GA (10:0)	55.0	73.44±0.01[e]	20.35±0.01[b]	79.67±0.09[c]
sCL11082	1:10	MD:GA (8:2)	55.5	74.64±0.01[d]	19.93±0.01[c]	88.08±0.05[b]
sCL11064	1:10	MD:GA (6:4)	60.5	72.32±0.00[f]	25.51±0.09[a]	89.25±0.08[a]

Note CM; Curcumin microencapsules, MD; Maltodextrin, GA; Gum Arabic, L^*; Lightness, a^*; Redness to greenness, and b^*; Yellowness to blueness

[a-f]: Value in the same row with different superscripts are significantly different ($p<0.05$)

4.5.1.3 Morphology of curcumin microencapsules

Scanning electron microscopy (SEM) was used to analyze the morphological structure of curcumin microencapsules particles presented in Figure 4.6. According to the results, the curcumin microencapsules produced by the spray-drying technique had a spherical morphology with wrinkles and vacancies, characteristics of powders that have been spray-drying. Furthermore, the SEM analysis of the morphological structure of six curcumin microencapsules formulas shows that the microcapsules lack sharp edges and curcumin sheet structure, suggesting that the wall matrix shielded the curcumin.

4.5.1.4 Physicochemical characteristics of curcumin microencapsules

Physicochemical characteristics of curcumin microencapsules, including bulk density, tap density, flowability, cohesiveness, moisture content, water activity, and hygroscopicity, are shown in Table 4.7. All six formulations of curcumin microencapsules had bulk densities ranging from 0.18 to 0.24 g/mL. The tap densities of the samples varied from 0.27 to 0.31 g/mL. Also investigated were the microcapsules flow characteristics as represented by the Carr's index (%) and Hausner ratio. With flow characteristics of the encapsulated curcumin exceeding the predicted standard a Carr's index of 30.77-47.82% and a Hausner ratio of 1.31-1.48, all of the curcumin microencapsules samples were viscous and poorly flowing. All six curcumin formulations had a moisture content ranging from 3.43 to 5.63% and a water activity percentage ranging from 0.17 to 0.25%. Furthermore, the curcumin microencapsules had comparatively low hygroscopicity values, ranging from 8.43 to 12.61%.

4.5.1.5 The solubility of curcumin microencapsules

Curcumin microencapsules demonstrated strong solubility in the water solubility test, ranging from 78.42 to 87.27% (Table 4.7). Figure 4.7, which tested for solubility with water as a solvent at room temperature, demonstrates that all six formulations of curcumin microencapsules showed increased solubility when compared to free curcumin (*Curcuma longa* extract). This suggests that the solubility of encapsulated curcumin was further improved to have higher solubility.

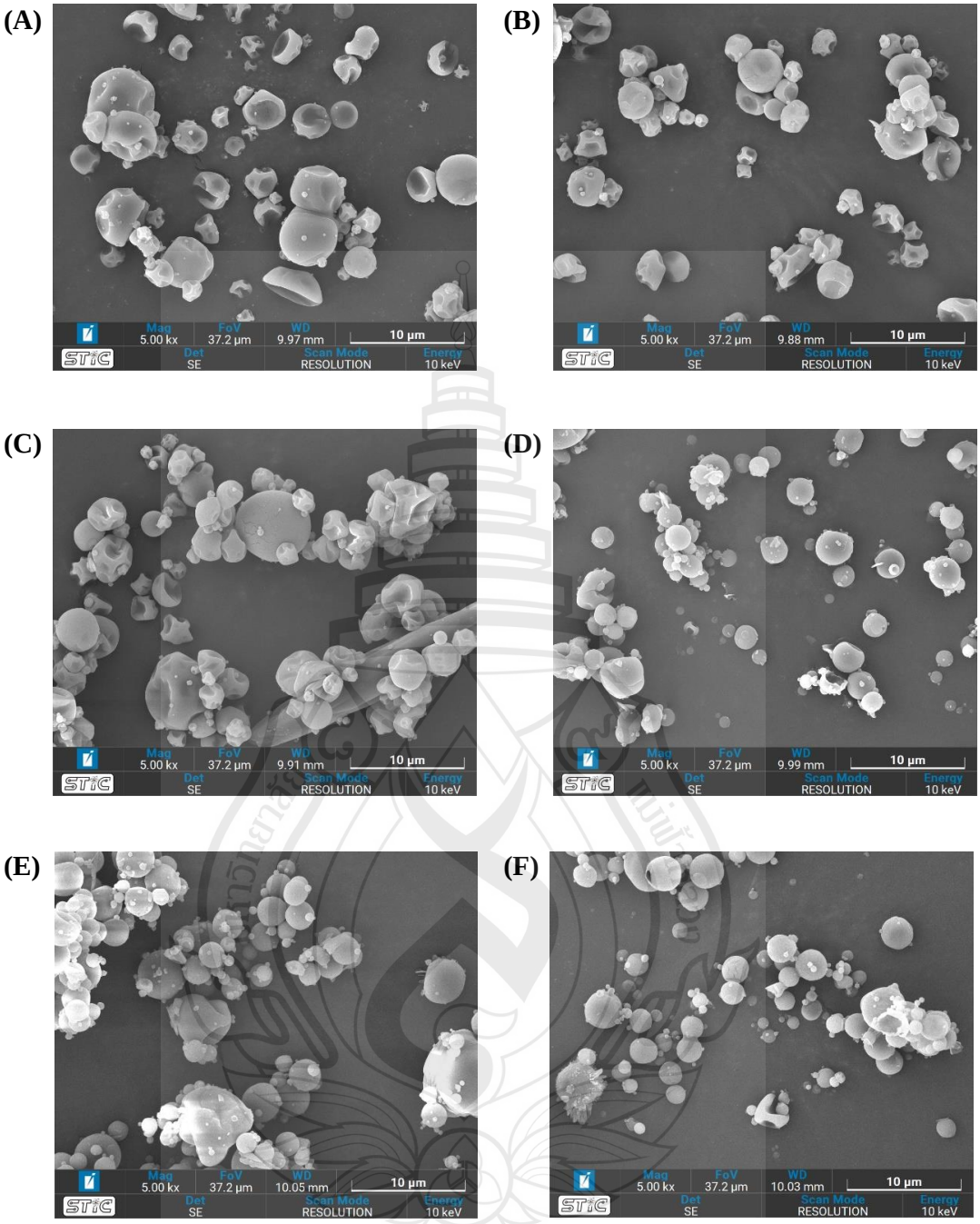


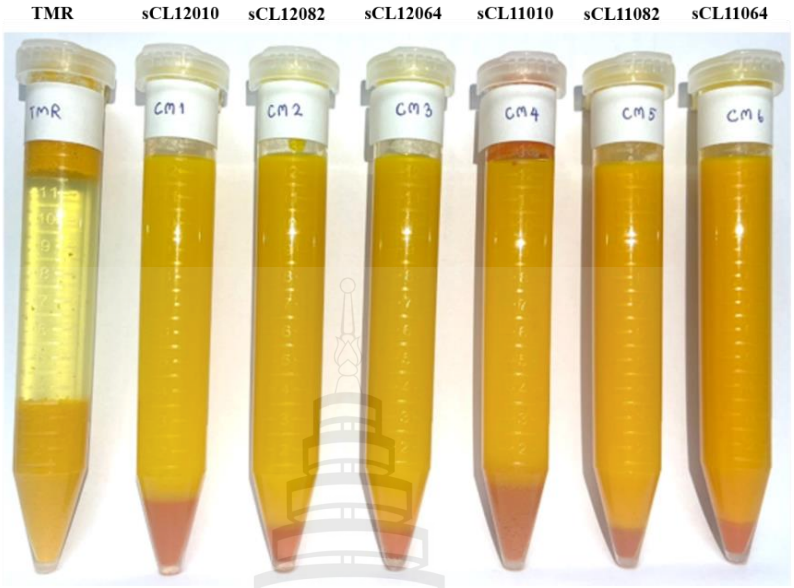
Figure 4.6 Scanning electron micrographs (SEM) of spray-dried curcumin microencapsules, (A) sCL12010, (B) sCL12082, (C) sCL12064, (D) sCL11010, (E) sCL11082, and (F) sCL11064

Table 4.7 Physicochemical properties of spray-dried curcumin microencapsules

Treatment code	Bulk density (g/mL)	Tap density (g/mL)	Flowability CI (%)	Cohesiveness (HR)	Moisture content (%)	Water activity (%)	Hygroscopicity (%)	WSI (%)
sCL12010	0.23 ± 0.01^{cd}	0.31 ± 0.01^{b}	37.32 ± 1.74^{c}	1.37 ± 0.02^{c}	3.47 ± 0.02^{a}	0.20 ± 0.00^{c}	12.65 ± 0.22^{b}	85.93 ± 0.63^{c}
sCLl2082	0.24 ± 0.00^{d}	0.31 ± 0.00^{b}	30.77 ± 0.00^{a}	1.31 ± 0.00^{a}	3.43 ± 0.12^{a}	0.17 ± 0.00^{a}	13.74 ± 0.36^{cd}	87.27 ± 0.85^{d}
sCL12064	0.22 ± 0.01^{c}	0.30 ± 0.01^{b}	34.51 ± 1.19^{b}	1.34 ± 0.02^{b}	3.44 ± 0.18^{a}	0.19 ± 0.00^{c}	14.46 ± 0.52^{d}	86.98 ± 0.31^{d}
sCL11010	0.18 ± 0.01^{a}	0.27 ± 0.01^{a}	47.82 ± 1.03^{e}	1.48 ± 0.01^{e}	5.63 ± 0.32^{d}	0.25 ± 0.00^{e}	8.43 ± 0.76^{a}	78.42 ± 0.07^{a}
sCL11082	0.20 ± 0.01^{b}	0.28 ± 0.01^{a}	36.46 ± 0.59^{bc}	1.36 ± 0.01^{c}	3.71 ± 0.11^{b}	0.19 ± 0.00^{b}	12.61 ± 0.52^{b}	84.25 ± 0.72^{b}
sCL11064	0.20 ± 0.01^{ab}	0.28 ± 0.01^{a}	42.01 ± 1.19^{d}	1.42 ± 0.01^{d}	4.79 ± 0.12^{c}	0.22 ± 0.00^{d}	13.48 ± 0.06^{c}	83.38 ± 0.27^{b}

Note CM; Curcumin microencapsules, CI; Carr's index, HR; Hausner ratio, and WSI; Water solubility index

$^{a\text{-}e}$: Values in the same row with different superscripts are significantly different ($p<0.05$)



Note TMR; *Curcuma longa* extract, CM1; sCL12010, CM2; sCL12082, CM3; sCL12064, CM4; sCL11010, CM5; sCL11082, and CM6; sCL11064

Figure 4.7 The solubility efficiency of curcumin microencapsules

4.5.2 Evaluation of *in vitro* Antioxidant Capacities of Curcumin Microencapsules

4.5.2.1 Metal chelating assay (MCA)

This study determines the transition metal binding value %inhibition by analyzing 6 formula curcumin microencapsules for their ability to transition metal that catalyzes oxidation reactions. The results found that sCL12064 had the highest ability to bind to transition metals, followed by CL11064 and sCL12010, all of which had %inhibition values of 64.65±1.75, 62.66±3.29, and 61.52±0.87, respectively. These results were statistically significant at $p<0.05$ (Table 4.8). The 50% inhibitory concentration (IC_{50}) of the ferrous ion ferrozine complex. Based on the results, it was found that sCL12082 had the strongest ability to bind to transition metals, followed by sCL11010 and sCL11082, with IC_{50} values of 0.06±0.01, 0.07±0.01, and 0.10±0.02 mg/mL, respectively. The results demonstrated statistical significance at $p<0.05$, as shown in Table 4.9.

4.5.2.2 DPPH radical scavenging activity

Assessment of the DPPH antioxidant capacity of extracts from 6 formula curcumin microencapsules, with results expressed as a percentage of DPPH free radical

inhibition. Extracts with a high DPPH free radical inhibition were found. sCL12082 exhibited the highest %inhibition value, followed by sCL11064 and sCL11082, all of which had %inhibition values of 70.72±3.39, 59.89±3.31, and 59.86±1.12, respectively. These results were statistically significant at $p<0.05$ (Table 4.8). The 50% inhibition concentration (IC_{50}) of the DPPH antioxidant capacity. Based on the results, it was found that sCL11010 had the strongest inhibited free radical DPPH, followed by sCL11082 and sCL11064 with IC_{50} values of 0.17±0.00, 0.38±0.10, and 0.42±0.02 mg/mL, respectively. The results demonstrated statistical significance at $p<0.05$, as shown in Table 4.9.

4.5.2.3 ABTS radical scavenging activity

Assessment of the ABTS antioxidant capacity of extracts from 6 formula curcumin microencapsules, with results expressed as a percentage of ABTS free radical inhibition. Extracts with a high ABTS free radical inhibition were found. sCL12082 exhibited the highest %inhibition value, followed by sCL11064 and sCL11082, all of which %inhibition values of 105.22±1.73, 87.58, and 81.72±3.24, respectively. These results were statistically significant at $p<0.05$ (Table 4.8). The 50% inhibition concentration (IC_{50}) of the ABTS antioxidant capacity. Based on the results, it was found that sCL12082 had the strongest inhibited free radical ABTS, followed by sCL11010 and sCL11064 with IC_{50} values of 0.27±0.08, 0.30±0.03, and 0.47±0.03 mg/mL, respectively. The results demonstrated statistical significance at $p<0.05$, as shown in Table 4.9.

4.5.2.4 Ferric reducing antioxidant power (FRAP)

Examination of extracts' ability to reduce transition metal levels from 6 formula curcumin microencapsules. Ability values will be reduced as a result and reported. Transition metals are expressed as ferrous micromoles per microgram of extract. sCL11010 was found to have the highest ability to reduce transition metals, followed by sCL11064 and sCL12064. This is a value of 28.95±1.47, 22.88±1.05, and 19.37±1.93 μM $FeSO_4$/mg, and it is statistically significant at $p<0.05$ (Table 4.8).

4.5.2.5 Nitro blue tetrazolium assay (NBT)

Examination of the antioxidant activity of superoxide anion of 6 formula curcumin microcapsules using the nitro blue tetrazolium test. The results will be expressed as the superoxide anion inhibition percentage of free radicals (%inhibition).

sCL12082 was shown to have the best ability to suppress superoxide anion free radicals, followed by sCL12064 and sCL11082. The value is 93.84±1.55, 93.24±3.76, and 85.32±2.01, with statistical at $p<0.05$ (Table 4.8). The 50% inhibition concentration (IC_{50}) inhibition of superoxide anion radicals. Based on the results, it was found that sCL11064 has the highest ability superoxide anions, followed by sCL12010 and sCL11082 with IC_{50} values of 0.03±0.17, 0.05±0.06, and 0.07±0.02 mg/mL, respectively. These results were statistically significant at $p<0.05$, as shown in Table 4.9.

4.5.2.6 Oxygen radical absorbance capacity (ORAC)

Analysis of six different curcumin microencapsules formulae' oxygen radical absorbance capacity. The results are reported as a micromolar of Trolox per microgram of extract. The peroxyl antioxidant capacity of the curcumin microencapsules with the highest ability to inhibit peroxyl free radicals was sCL11082, followed by sCL11064 and sCL12010 with statistical significance at $p<0.05$. These extracts had the capacity to resist peroxyl radicals equal to 0.77±0.01, 0.75±0.01, and 0.74±0.03 µM of TE/µg of extract, respectively. This is comparable to *Curcumin longa* extract's peroxyl antioxidant capacity. It is equivalent to 0.78±0.01 µM of TE/µg of extract in terms of antioxidant ability, as shown in Figure 4.8 and Figure 4.9.

After analyzing the six curcumin microencapsules to the effectiveness of *Curcuma longa* extract, it is demonstrated by the test results of the various properties of the microencapsules such as external appearance, encapsulation yields, color values, morphology, physicochemical characteristics, water solubility, and *in vitro* antioxidant capacities that their all have good properties. The MCA, DPPH, ABTS, FRAP, NBT, and ORAC tests show that sCL11064 has strong antioxidant capacities. Consequently, the quantity of curcuminoid extracts in sCL11064 will be measured to verify the precision and accuracy of the test that will be conducted at the experimental *in vivo* level.

Table 4.8 Total antioxidant capacities of curcumin microencapsules

Treatment code	**Metal chelating**[1] **(%inhibition±SD)**	**DPPH**[2] **(%inhibition±SD)**	**ABTS**[3] **(%inhibition±SD)**	**FRAP**[4] **(μM $FeSO_4$/mg)**	**NBT**[5] **(%inhibition±SD)**
Curcuma longa	38.62±2.49^{c}	108.36±2.35^{a}	102.99±0.23^{a}	30.22±2.27^{a}	123.77±0.72^{a}
sCL12010	61.52±0.87^{a}	47.39±4.15^{d}	58.42±1.52^{e}	16.85±0.10^{c}	50.50±4.90^{d}
sCL12082	61.42±1.28^{a}	70.72±3.39^{b}	105.22±1.73^{a}	17.25±0.65^{c}	93.84±1.55^{b}
sCL12064	64.65±1.75^{a}	47.36±1.25^{d}	62.28±2.30^{d}	19.37±1.93^{c}	93.24±3.76^{b}
sCL11010	52.41±4.28^{b}	58.90±0.46^{c}	78.73±3.27^{c}	28.95±1.47^{a}	84.69±8.02^{c}
sCL11082	50.57±1.99^{b}	59.86±1.12^{c}	81.72±3.24^{c}	18.93±0.49^{c}	85.32±2.01^{c}
sCL11064	62.66±3.29^{a}	59.89±3.31^{c}	87.58±1.33^{b}	22.88±1.05^{b}	78.41±1.40^{c}

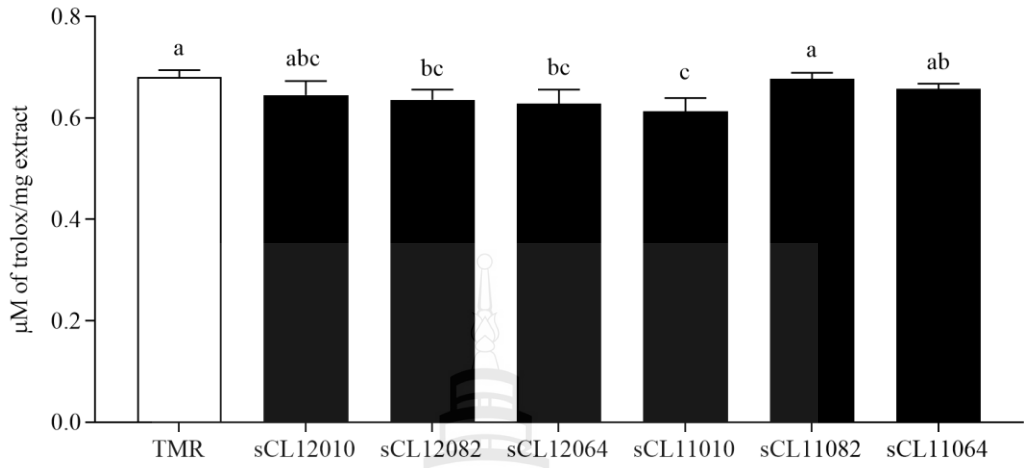
Note [1]: Preventive properties metal chelating activity (MCA) of extracts were expressed percentage chelating capacity (%inhibition), [2,3]: Free radical scavenging activities of extracts were expressed interns of their inhibitory activity against DPPH and ABTS+ radicals (%inhibition), [4,5]: Single electron transfer of the ferric reducing antioxidant power (FRAP) and superoxide anion radical by the nitro blue tetrazolium (NBT) were expressed as micromoles of ferrous per mg of extract and inhibitory activity, respectively [a-d]: Values in the same row with different superscripts are significantly different ($p<0.05$)

Table 4.9 The antioxidant capacities of curcumin microencapsules

Treatment code	**Metal chelating**[1] **(IC_{50}; mg/mL)**	**DPPH**[2] **(IC_{50}; mg/mL)**	**ABTS**[3] **(IC_{50}; mg/mL)**	**NBT**[4] **(IC_{50}; mg/mL)**
Curcuma longa	0.06±0.00^{a}	0.42±0.02^{a}	0.18±0.01^{a}	0.38±0.07^{d}
sCL12010	0.24±0.05^{d}	1.17±0.03^{a}	0.66±0.01^{c}	0.05±0.06^{a}
sCL12082	0.06±0.01^{a}	0.91±0.01^{d}	0.27±0.08^{b}	0.55±0.36^{a}
sCL12064	0.12±0.03^{b}	1.55±0.06^{c}	0.53±0.00^{cd}	0.29±0.44^{a}
sCL11010	0.07±0.01^{ab}	0.58±0.06^{c}	0.30±0.03^{b}	3.62±3.94^{b}
sCL11082	0.10±0.02^{ab}	0.63±0.06^{ab}	0.47±0.03^{c}	0.07±0.02^{a}
sCL11064	0.17±0.03^{c}	0.89±0.14^{c}	0.54±0.03^{d}	0.03±0.17^{a}

Note [1]: Preventive properties metal chelating activity (MCA) of extracts were expressed as the amounts that inhibited the ferrous ion ferrozine complex by 50% (IC_{50}; mg/mL), [2,3]: Free radical scavenging activities of extracts were expressed as the concentration caused 50% inhibition of DPPH and ABTS+ radicals (IC_{50}; mg/mL), and [4]: Single electron transfer of the superoxide anion radical by the nitro blue tetrazolium (NBT) were expressed as the concentration that caused 50% inhibition of superoxide anion radicals (IC_{50}; mg/mL)

[a-d]: Values in the same row with different superscripts are significantly different ($p<0.05$)



Note TMR; *Curcuma longa* extract

Figure 4.8 The antioxidant capacity of curcumin microencapsules was determined by the ORAC assay. Data are shown as the mean ± SD, values with different letters indicate significantly different ($p<0.05$).

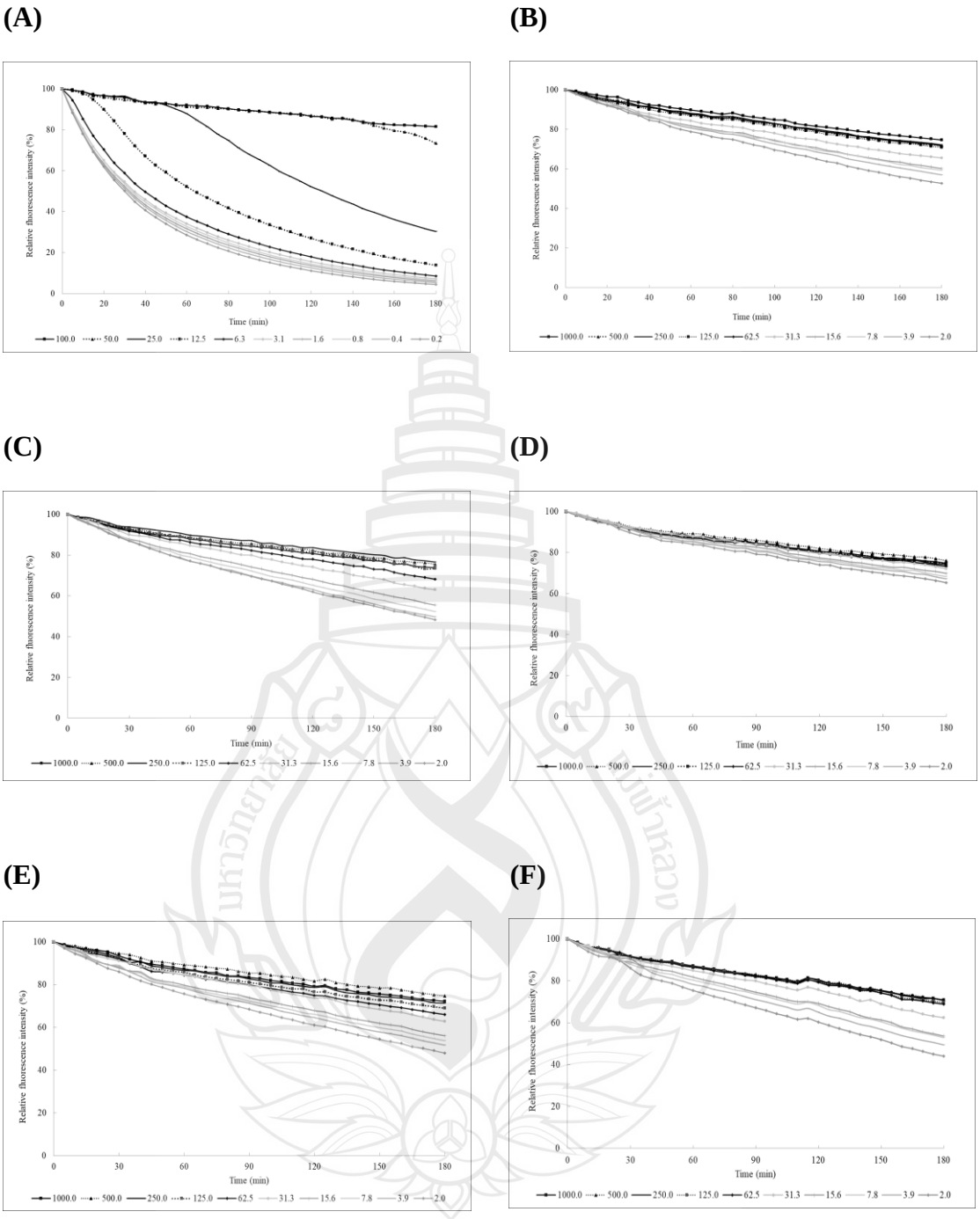


Figure 4.9 ORAC fluorescence decay curves of fluorescein, in the presence of (A) Trolox, (B) *Curcuma longa* extract, (C) sCL12010, (D) sCL12082, (E) sCL12064, (F) sCL11010, (G) sCL110825, and (H) sCL11064

(G) **(H)**

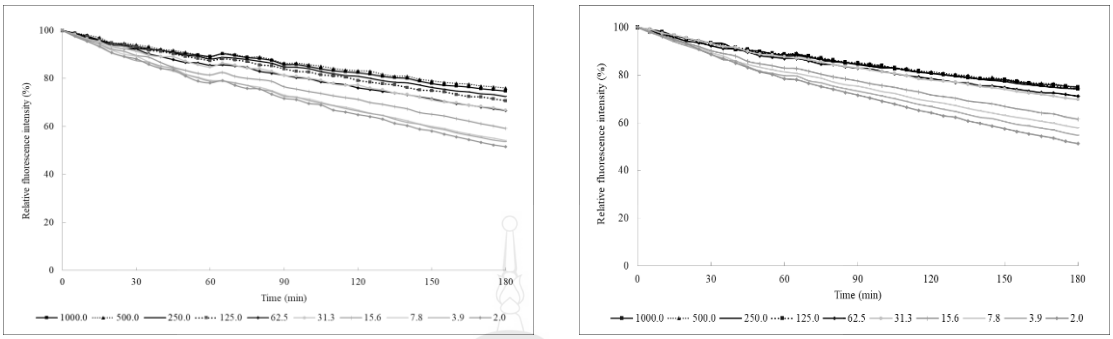


Figure 4.9 (continued)

4.5.3 Active Constituents of the Formulation of Microencapsulation

4.5.3.1 Total phenolic content (TPC)

The total phenolic content of 6 formula curcumin microencapsules was analyzed, and the results were reported as mg of gallic acid equivalent per g of extract. The results showed that sCL11010 had the highest phenolic content, followed by sCL11064 and sCL12064, with statistical significance at $p<0.05$. These values are 366.90±30.32, 346.36±24.00, and 282.04±19.46 mg of gallic acid equivalent/g of extract, respectively. As shown in Table 4.10.

4.5.3.2 Total flavonoid content (TFC)

The total flavonoid content of 6 formula curcumin microencapsules was analyzed, and the results were reported as mg of catechin equivalence per g of extract. The results showed that sCL12082 had the highest phenolic content, followed by sCL11064 and sCL11082, with statistical significance at $p<0.05$. These values are 122.64±5.95, 91.14±5.96, and 89.08±4.23 mg of catechin equivalence/g of extract, respectively. As shown in Table 4.10.

The total phenolic and total flavonoid analysis of the chemical marker quantification showed that sCL11064 had high total phenolic and total flavonoid contents, which were by the results of the antioxidant activity test previously reported.

4.5.3.3 Quantification of curcuminoid content of curcumin microencapsules

Curcumin contains three curcuminoids, of curcumin, DMC, and Bis-DMC. Curcumin is the bright orange-yellow pigment found in curcumin. *Curcuma longa* extract that was microencapsulated was separated using column chromatography and identified using HPLC in order to quantify these three curcuminoids. Peak appeared at retention times of the HPLC analysis of curcumin, DMC, and Bis-DMC, 12.63±0.12, 11.68±0.11, and 10.80±0.09 minutes, respectively (Figure 4.10A).

The amount of curcuminoid on different samples was calculated using calibration curves. Curcumin, DMC, and Bis-DMC were injected four times independently at seven concentrations relative to the peak areas to create the calibration curves. High accuracy and reproducibility were found in the linearity in the concentration range of 2.87 to 100.26 ppm (Figure B1). The results of the regression analysis demonstrated a linear relationship between the experimental data points and

curcumin, DMC, and Bis-DMC, with excellent correlation coefficients (R^2) of 0.9997, 0.9999, and 0.9995, respectively.

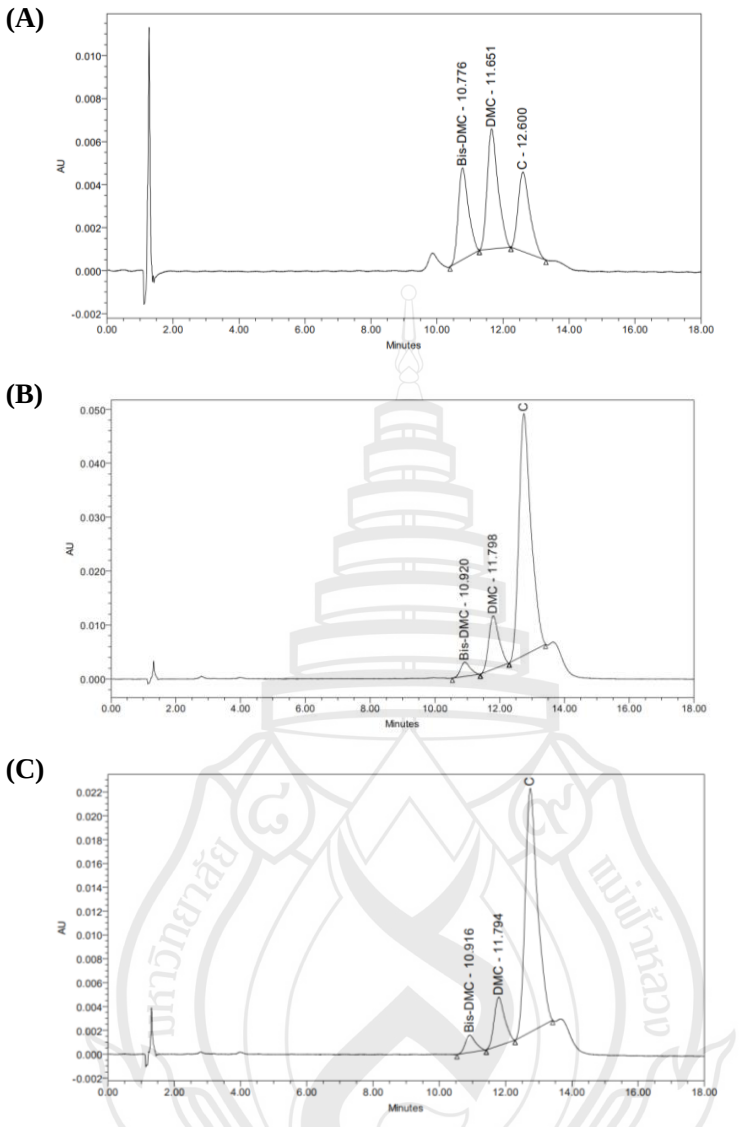
The major compound in the *Curcuma longa* extract that was compared with the microencapsulated form of all tested curcumins was curcumin as shown in Figure 4.10 B and C, the secondary two peaks were DMC, and Bis-DMC, respectively. Figure 4.11 presents an overview of the curcuminoid composition of the *Curcuma longa* extract and the curcumin microencapsulated by HPLC, showed the following curcuminoid contents: curcumin 69.83±2.00 and 31.12±0.00 mg/kg, DMC 10.08±0.28 and 4.42±0.10 mg/kg, and Bis-DMC 4.22±0.09 and 2.88±0.04 mg/kg, respectively.

Table 4.10 The main active ingredients of curcumin microencapsules

Treatment code	**Phenolic**[1] **(mg gallic acid/ g of extract)**	**Flavonoid**[2] **(mg catechin/ g of extract)**
Curcuma longa	514.13±50.55[a]	185.22±8.87[a]
sCL12010	278.17±26.20[c]	61.13±2.78[c]
sCL12082	289.79±26.58[c]	122.64±5.95[b]
sCL12064	282.04±19.46[c]	82.59±5.93[b]
sCL11010	366.90±30.32[b]	82.03±2.47[c]
sCL11082	270.80±18.93[c]	89.08±4.23[c]
sCL11064	346.36±24.00[b]	91.14±5.96[c]

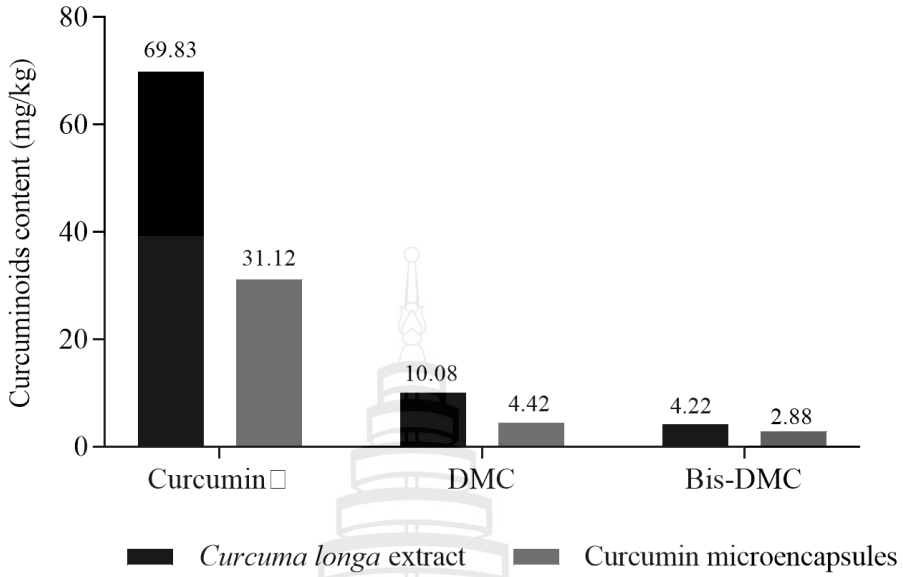
Note [1,2]: Total phenolic content (TPC) and total flavonoid content (TFC)

[a-c]: Values in the same row with different superscripts are significantly different ($p<0.05$)



Note C; curcumin, DMC; Demethoxycurcumin, and Bis-DMC; Bisdemethoxycurcumin

Figure 4.10 HPLC chromatographic separation of extract. (A) Standard solution, (B) *Curcuma longa* extract, and (C) Curcumin microencapsules (sCL11064)



Note DMC; Demethoxycurcumin, and Bis-DMC; Bisdemethoxycurcumin

Figure 4.11 The amount of curcuminoid contained in *Curcuma longa* extract and curcumin microencapsules (sCL11064)

4.6 Neuroprotective Mechanisms of Microencapsules Containing Standardized *Curcuma longa* Extract

4.6.1 Curcumin Microencapsulation's Effects for Toxicity Tests in *C. elegans*

4.6.1.1 Food clearance assay

The toxicity testing of sCL11064 at various concentrations by measuring the absorbance from the decreased turbidity of *E. coli* OP50 in the liquid medium used to cultivate *C. elegans* for 7 days (Figure 4.12A). The results show that sCL11064 at concentrations of 100, 250, 500, and 1,000 µg/mL did not affect *C. elegans'* feeding behavior compared to the control group ($p<0.05$). As shown in Figure 4.12B.

4.6.1.2 Pharyngeal Pumping Rate

According to an evaluation of the feeding rate of sCL11064 at various concentrations, the number of contractions and relaxations of the pharyngeal muscles of *C. elegans* in 1 minute (Figure 4.12C). The results show that the pharyngeal pumping rate of *C. elegans* was not affected by sCL11064 at concentrations of 100, 250, 500, and 1,000 µg/mL compared to the control group ($p<0.05$). As shown in Figure 4.12D.

4.6.2 Protective Effects of Curcumin Microencapsulate Against Paraquat-Induced Oxidative stress in *C. elegans*

When determining the survival rate of *C. elegans* under oxidative stress-induced paraquat at a concentration of 50 mM, the result was discovered that sCL11064 significantly increased the survival rate and mean lifespan in a dose-dependent manner at concentrations between 100-1000 µg/mL, as shown in Figure 4.13. The highest effect on *C. elegans* survival under oxidative stress was induced by sCL11064 at a concentration of 250 µg/mL; the mean and median survival rates were 220.09±6.69 and 276.00±18.33 hours. This was followed by concentrations of 100 µg/mL (203.50±18.68 and 276.00±0.00 hours), 500 µg/mL (169.29±3.49 and 264.00±6.93 hours), and 1,000 µg/mL (119.03±33.81 and 204.00±52.31 hours), respectively (Figure 4.13A). When compared to the untreated control group, which had a mean lifespan of 230.00±6.93 hours, the groups treated with the sCL11064 at concentrations of 100, 250, 500 µg/m

had higher mean lifespans of 16.95%, 15.25%, and 13.56%, respectively (Figure 4.13B).

4.6.3 Neuroprotective Effects of Curcumin Microencapsulate in Transgenic *C. elegans* models

4.6.3.1 Curcumin microencapsulate protect DA neurons from 6-OHDA-induced neurodegeneration in BZ555

The fluorescence expression of the dopamine transporter marker *Pdat-1*:GFP in the BZ555 transgenic worms indicated the presence of DA neuronal morphology (Figure 4.14A). When 6-OHDA was administered to *C. elegans* DA neurons, degeneration was found in the GFP-tagged DA neurons. As shown in Figure 4.14, the GFP fluorescence intensity of ADE and CEP neurons in 6-OHDA-treated BZ555 worms was 65.69% of that of untreated nematodes, indicating that 6-OHDA is capable impair DA ($p<0.05$). When sCL11064 was administered to 6-OHDA-induced nematodes at concentrations of 100, 250, and 500 µg/mL, the GFP fluorescence intensity of DA neurons was 59.69%, 61.87%, and 59.55%, respectively. These results did not differ significantly from those of the 6-OHDA-treated control group. According to these results, sCL11064 at 100, 250, and 500 µg/mL did not decrease the dopaminergic neurodegeneration induced by 6-OHDA in the *C. elegans* model.

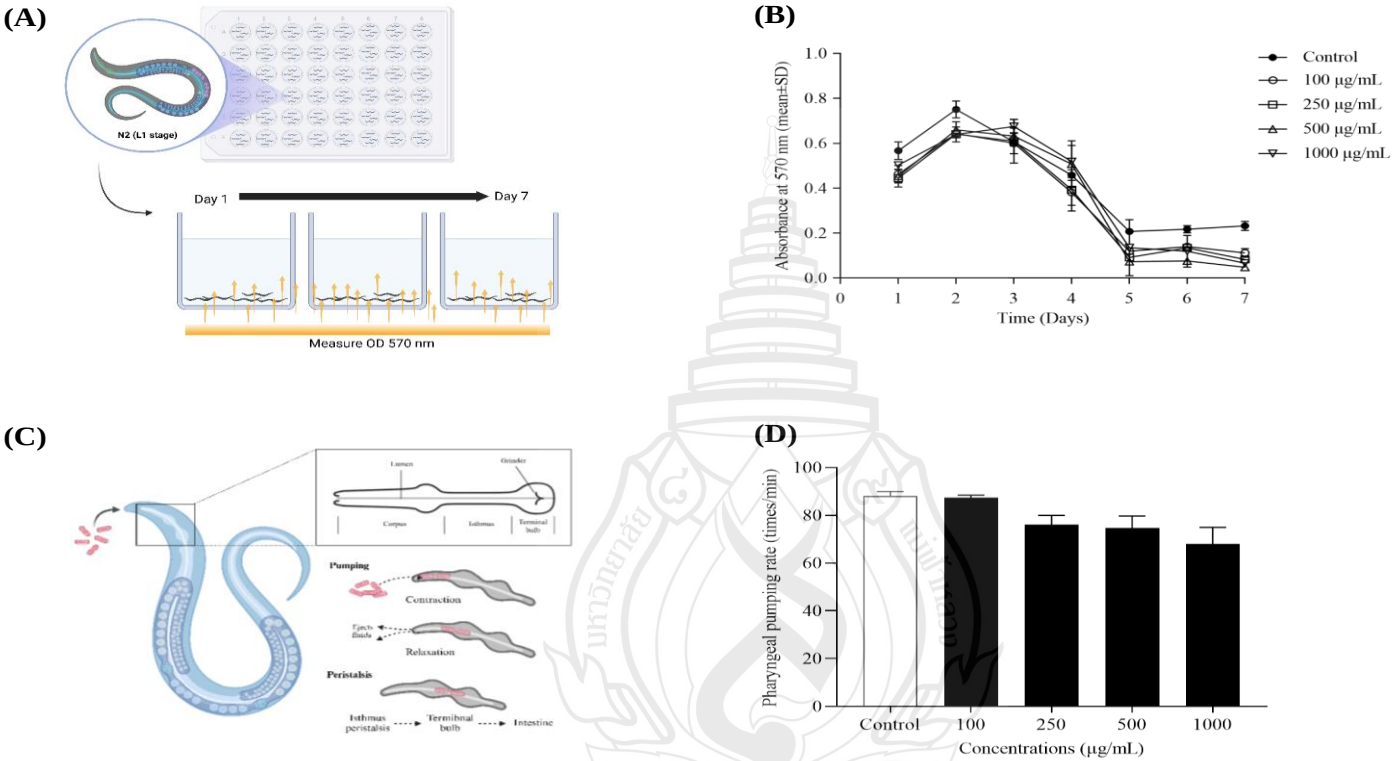


Figure 4.12 Effect of sCL11064 on food-intake behavior of *C. elegans*, (A) Schematic of *C. elegans*-based food intake assay, measuring OD570 nm on day 1 to day 7, (B) Bacteria clearance assay for testing concentration of CM6, (C) The anatomy and typical motions of the *C. elegans* pharynx: pumping and peristalsis, and (D) Pharyngeal pumping rate of *C. elegans* with or without sCL11064 treatment. Data is shown as mean±SD of three independent experiments, $p<0.05$.

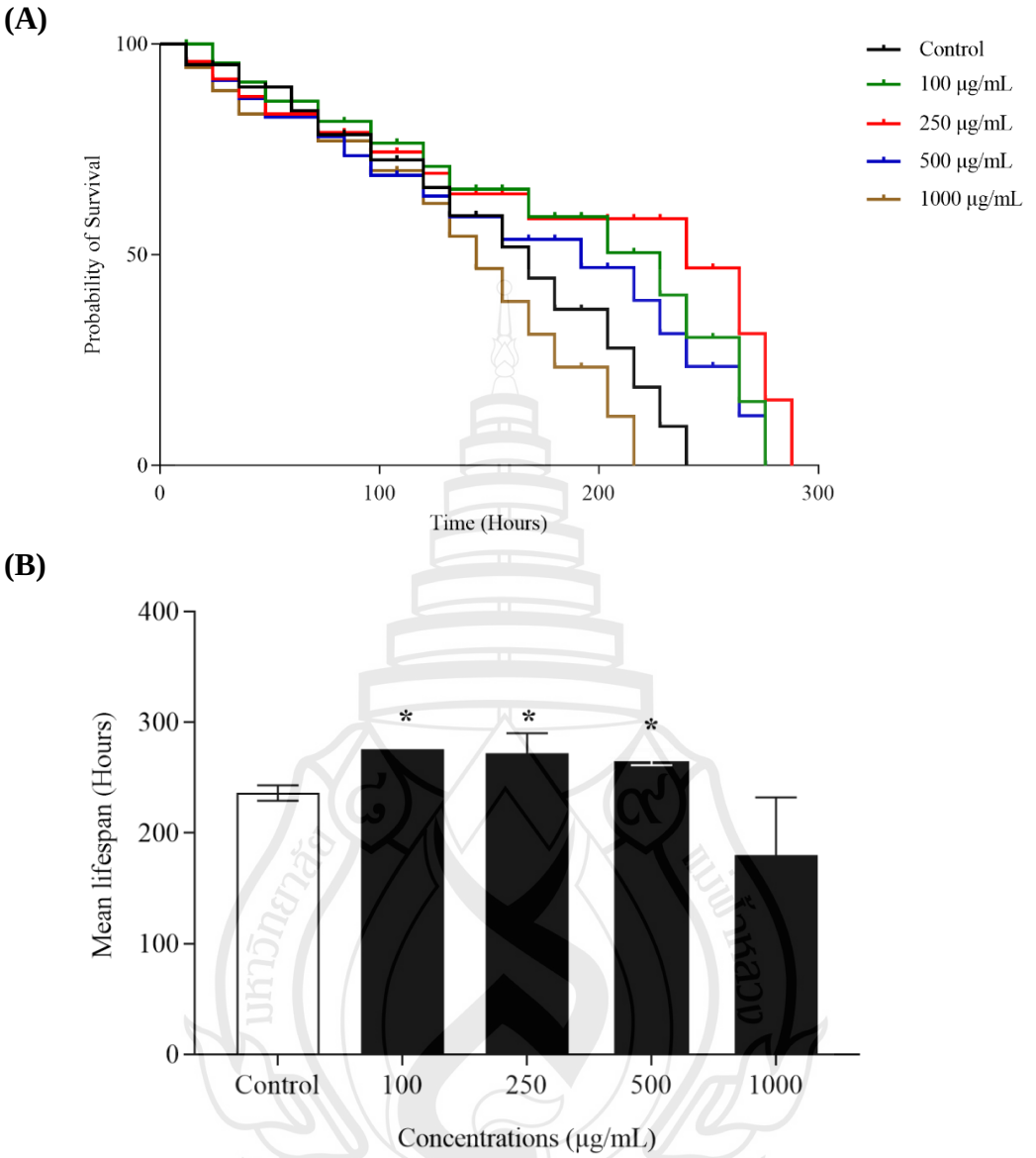


Figure 4.13 Effect of sCL11064 on survival rates of paraquat-treated *C. elegans*. (A) Representative Log-lank (Mantel-Cox) survival curves, and (B) Mean lifespan of *C. elegans* with or without sCL11064 treatment are shown from three independent experiments. * $p<0.05$ as compared to control.

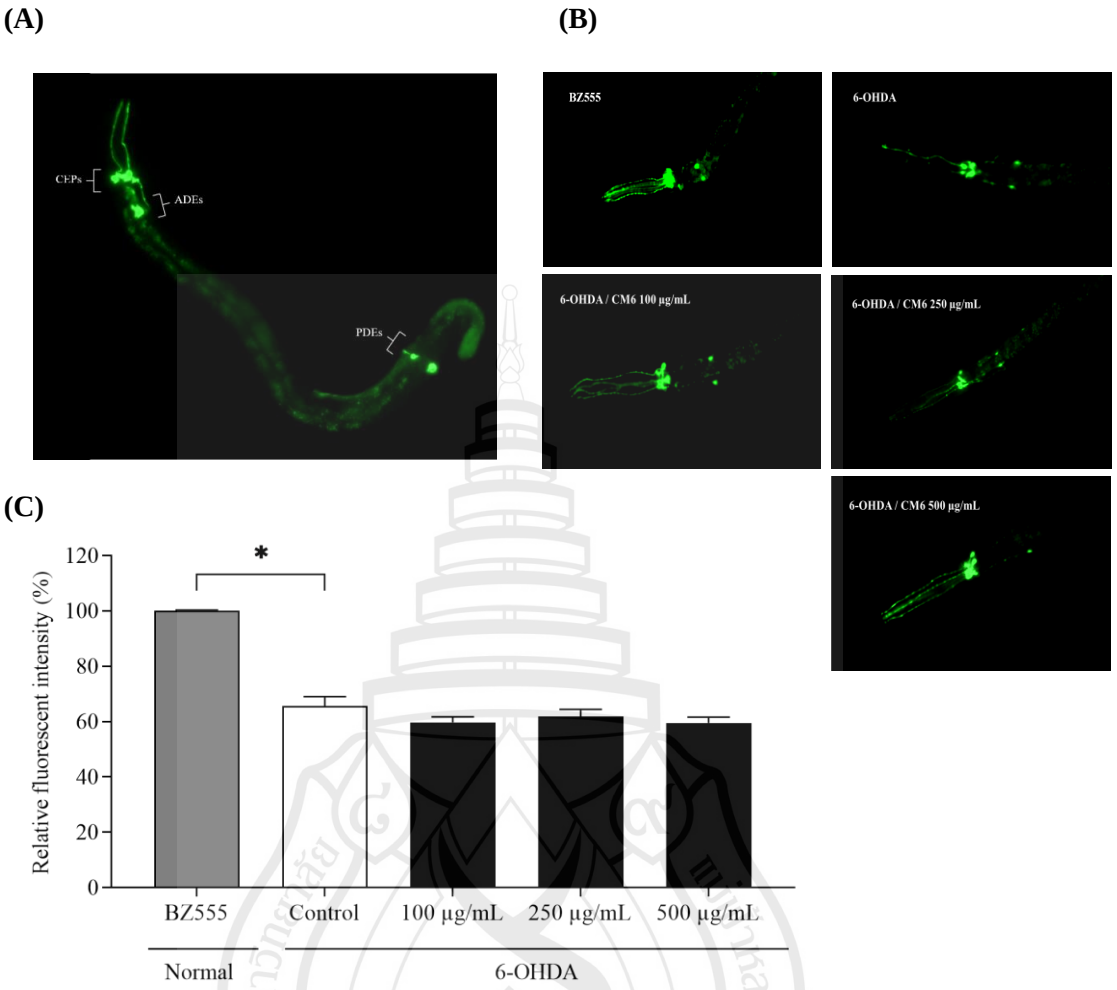


Figure 4.14 Effect of sCL11064 on the 6-OHDA-induced degeneration of dopaminergic (DA) neurons in *C. elegans*. (A) Eight neurons are depicted in the architecture of DA in *C. elegans* strain BZ555. Four cephalic (CEPs) neurons in the head, two anterior deirid (ADE) neurons, and two posterior deirid (PDE) neurons produce cytosolic green fluorescent protein (GFP) *dat-1* promoter. (B) GFP expression pattern in DA neurons of control transgenic BZ555 strain and 100, 250, 500 µg/mL treated nematodes. (C) Graphical representation for fluorescence intensities of GFP expression in DA neurons of the nematodes treated with or without sCL11064. The data represent the mean±SD of three independent experiments. *$p<0.05$ as control compared BZ555 nematodes.

4.7 The Feasibility of Using the Produced Microencapsules as a Functional Food

4.7.1 Extruded Snacks of Curcumin Microencapsules

The development of the microencapsules that were produced as functional ingredients in the food industry was investigated using ready-to-eat (RTE) extruded snacks as a model food. Raw banana flour, pregelatinized rice flour, and 0.25% sCL11064 were the main ingredients used to make the novel extruded snacks in this study. It was found that the texture and color of the new snacks with curcumin microencapsules and the control type without curcumin microencapsules had comparable external and internal characteristics. there were no visible textural variations between the novel and control formulas. However, the snacks that included sCL11064 microencapsules had a significantly higher intensity of yellow color, as shown in Figure 4.15.

4.7.2 Nutritional Facts

The microencapsulated snack nutritional value calculation results were evaluated on 10 g snacks and presented as a percentage of the recommended daily intake and as the nutritional value per serving, as shown in Table 4.11. The snack's energy value, without energy from fat, was 366.20 kcal/100 g, according to the test findings. For the 100 g of snacks, this new food has 84.41 gof carbohydrates, 7.14 g of protein, 216.06 mg of sodium, 133.35 mg of calcium, and 2.57 mg of iron. Furthermore, per 100 g of snacks, the analyzed snacks had 2.50 g of fiber, 1.48 grams of ash, and 6.97 g of moisture.

4.7.3 Sensory Evaluation

Sensory evaluations of foods that have been extruded. The participant's general characteristics and health-related activities are shown in Table B1. The first consumer acceptance of the designed snacks was evaluated using the volunteers who exhibited regular food consumption behavior (RFCb; n=50) or healthy food consumption behavior (HFCb; n=50). With monthly incomes ranging from 15,000 to 45,000 baht, the majority of volunteers from both groups were between the ages of 20 and 49. The volunteers in the HFCb group were interested in extruded snack products with curcumin

microencapsulated as an ingredient, which was highly interesting to both the general group (90.20%) and the healthy group (94.12%). They also frequently are healthy food, abstained from alcohol, exercised more than three times a week, and had regular health checks.

According to the test results, HFCb volunteers scored significantly higher than RFCb volunteers on the sensory component of liking each panelist group's product attributes, as shown in Figure 4.16. Regarding overall flavor, there were no significant differences between the two groups' scores (7.4±1.2 for HFCb and 6.8±1.7 for RFCb). In the categories of overall acceptance, appearance, taste, texture, odor, and after-taste feeling, the HFCb group scored higher (7.2±14 to 8.0±1.0) than the RFCb group (6.5±1.5 to 7.5±1.4) (Table B2). Regarding panelists' acceptability of the product, it was found that both the HFCb and RFCb groups had equally high levels of acceptance (49.02%) (Figure 4.17A). Furthermore, the HFCb group expressed more interest in buying the product than the RFCb group, with interest levels of 56.86% and 47.06%, respectively (Figure 4.17B).

The result of a sensory test on willingness for the change to use the product showed that both the HFCb and RFCb sets of testers were equally satisfied with their willingness to switch, with a 37.25% level of satisfaction (Figure 4.17C). Taking into account the evaluation of the score for wanting to tell or recommend to friends, as shown in Figure 4.18, the difference between the sample group's total score, which was evaluated at 1-6 points, and the total scores of the HFCb and RFCb groups, which were evaluated at 9-10 points, was 43.10 for HFCb group, falling within the range where the test group is impressed and wants to tell others. The RFCb groups, on the other hand, had a difference of -36.27, which falls within the range where the test group is not satisfied. This indicates that this product has a high degree of recommendation and has potential for improvement for the HFCb and RFCb groups, respectively.

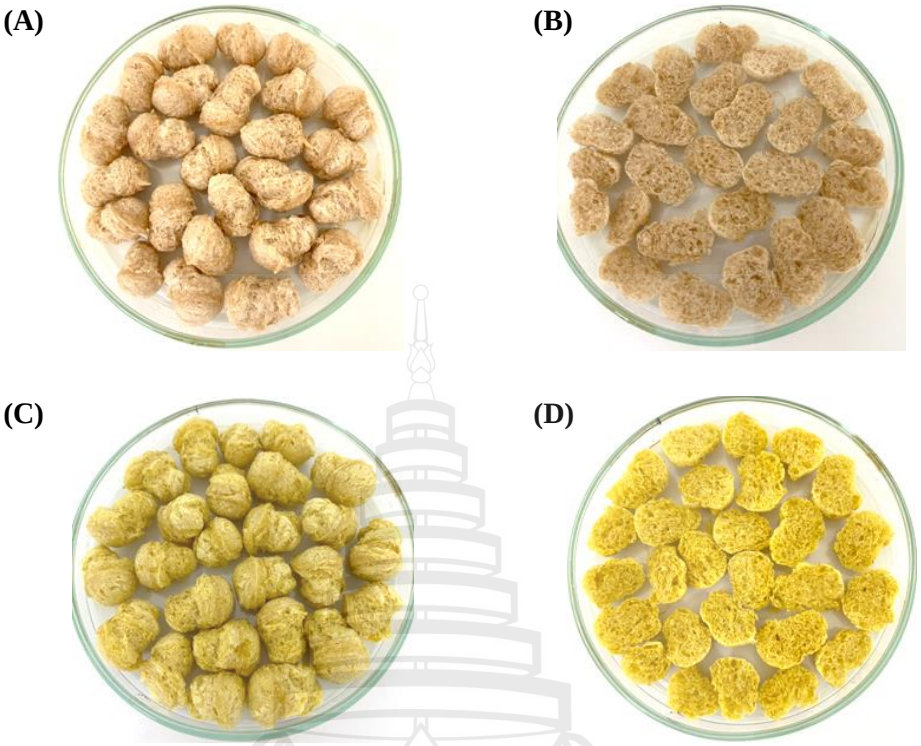
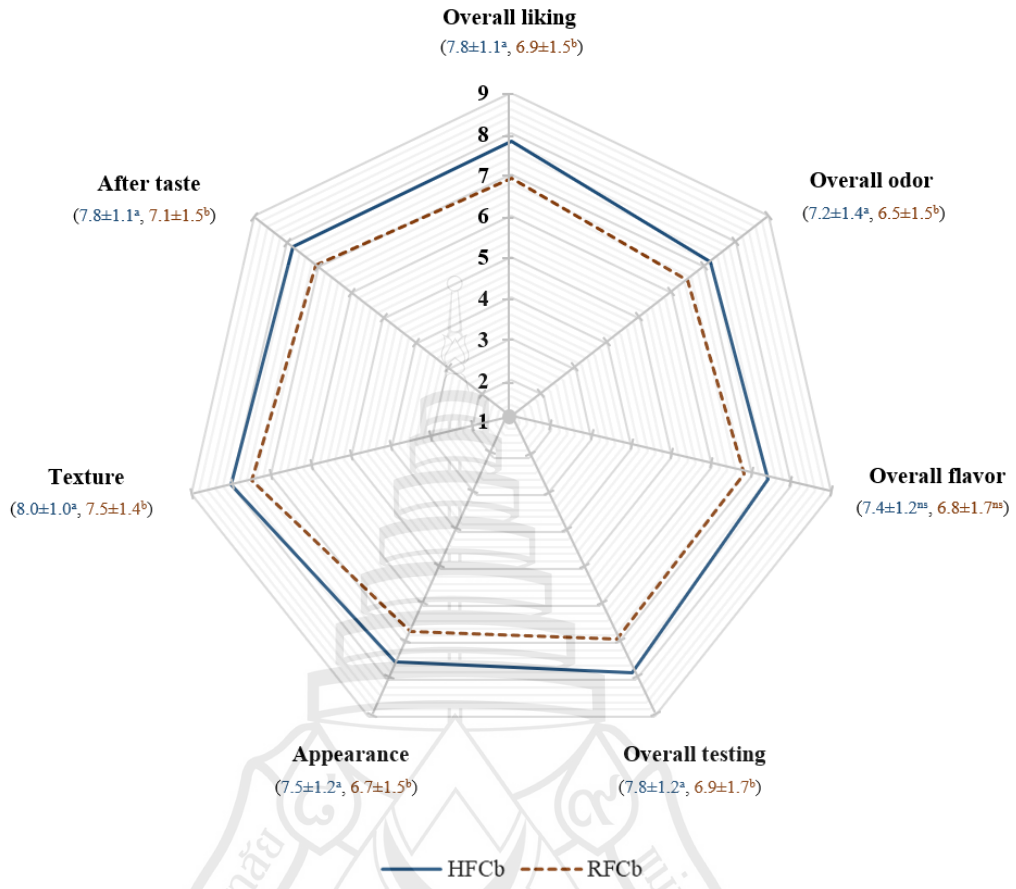


Figure 4.15 Appearance of functional food extruded snacks of curcumin microencapsules (sCL11064). (A) External appearance of control formula, (B) Internal appearance of control formula, (C) External the appearance of curcumin microencapsules, and (D) Internal appearance of curcumin microencapsules

Table 4.11 Total dietary content of extruded snacks from green banana-based curcumin microencapsules

Analysis item	**Result (per 100 g)**	**Serving size (10 g)**	**Thai RDI*** (%)
Total energy, kcal	366.20	35	
Energy from fat, kcal	0.00	0	
Total fat, g	0.00	0	0
Saturated fat	0.00	0	0
Cholesterol, mg	0.00	0	0
Protein (factor 6.25), g	7.14	<1	
Total carbohydrate, g	84.41	8	3
Dietary fiber, g	2.50	0	0
Sugars, g	0.88	0	
Sodium,mg	216.06	20	1
Vitamin A (Beta carotene), µg	0.00	(0.00)	0
Vitamin B1, mg	0.02	(0.00)	0
Vitamin B2, mg	0.00	(0.00)	0
Calcium, mg	133.35	(13.34)	<2
Iron, mg	2.57	0.26	<2
Ash, g	1.48		
Moisture, g	6.97		

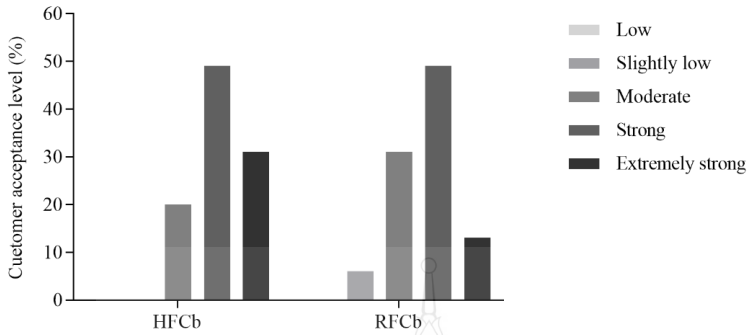
Note *; Percentage of recommended daily nutrient intake for Thai people aged 6 years and over, based on an energy requirement of 2,000 kcal per day



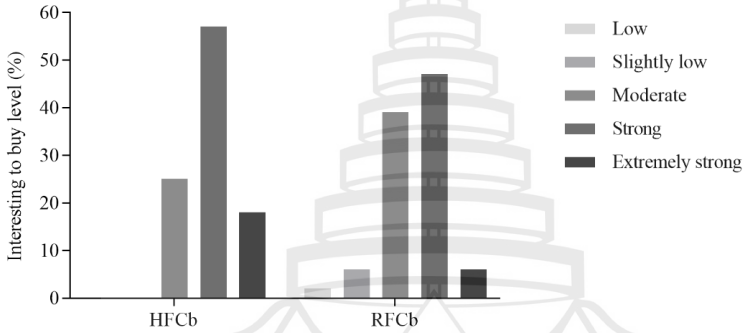
Note HFCb; Healthy food consumption behavior, RFCb; Regular food consumption behavior

Figure 4.16 Liking score for sensory properties of each group of testers towards the appearance of extruded snacks. ^{a,b}; The difference in the mean liking score of each group of testers was statistically significant ($p \leq 0.05$), and ^{ns}; No statistically significant difference in the mean liking score of each group of testers ($p > 0.05$).

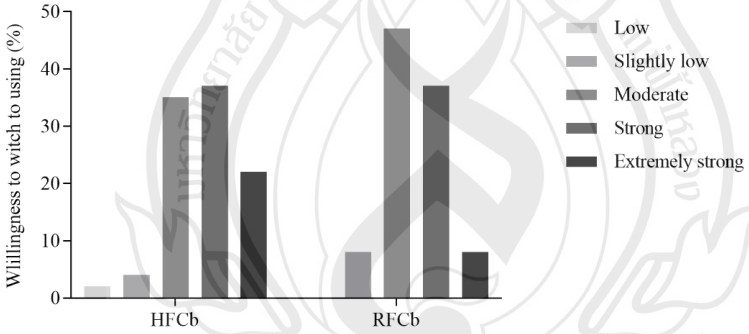
(A)



(B)



(C)



Note HFCb; Healthy food consumption behavior, RFCb; Regular food consumption behavior

Figure 4.17 Data on consumer acceptability of the product and willingness to switch to using extruded snacks. (A) Customer acceptance level, (B) Interest to buy level, and (C) Willingness to switch to using level.

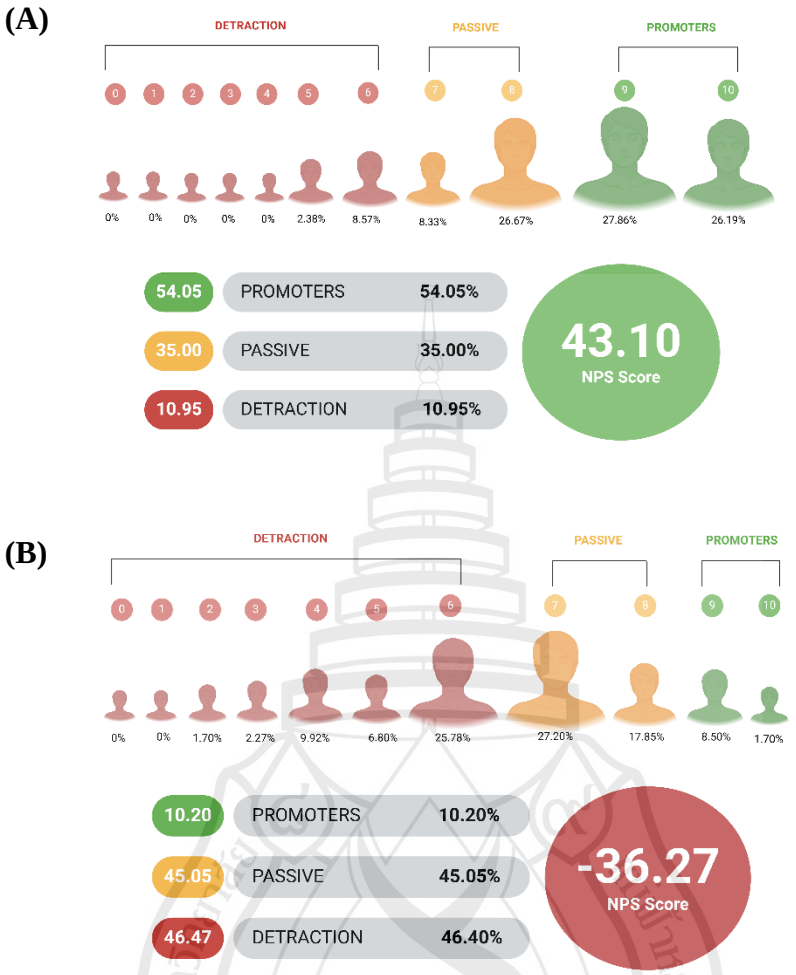


Figure 4.18 Results of Net Promoter Score (NPS) of the test group towards the extruded snacks, (A) Healthy food consumption behavior; HFCb and (B) Regular food consumption behavior; RFCb.

CHAPTER 5

DISCUSSION AND CONCLUSION

5.1 Discussion

Parkinson's disease (PD) is acknowledged as a major neurodegenerative disease is brought on the nervous system gradually degenerating with age, which results in gradually worsening movement and high rates of disability. Additionally, medicinal plants particularly plant antioxidants have been recognized for their phytochemical properties that might fend against such disease. The antioxidant and neuroprotective properties of medicinal plants that had been approved by the Thai FDA was the primary focus o this study's systematic review. A preliminary systematic review evaluation examined the biological activity and viability of 211 FDA-approved dietary supplements derived from medicinal plants; 153 were determined to be grown in Thailand, while the remaining 58 were not. According to a search of the Royal Botanic Gardens' Plants of the World Online, 43 species (20.37%) were native to that specific area (i.e. *Astragalus propinquus*, *Sambucus canadensis*, and *Turnera diffusa*), along with 13 species type of plants in the algae group (i.e. *Arthrospira mazima*, *Chlorella vulgaris*, and *Haematococcus pluvialis*), one coral species (*Lithothamnion calcareum*), and one species for which no information was provided (*Rubus ursinus*) (Kew science, 2024).

Of Thailand's 153 medicinal plants, the Asteraceae and Rosaceae families are the most common, followed by the Lamiaceae, Fabaceae, Poaceae, and Rutaceae families, in that order. The Asteraceae family is the largest plant family globally (Rolnik & Olas, 2021). Utilized extensively for therapeutic purposes, in specific, traditional medicine excellent antioxidant properties are present (Achika et al., 2014), such as *Taraxacum officinale*, *Artemisia absinthium*, and *Helianthus tuberosus*, (Anvari & Jamei, 2018; Rolnik et al., 2021; Piątkowska et al., 2022), including properties to neuroprotective effects, *Matricaria recutita*, *Flaveria bidentis*, and *Klasea centauroides* (Ranpariya et al., 2011; Cavallaro et al., 2018; Razuvaeva et al., 2023).

From the results of collecting such information, it was found that eleven plant families of all; Asteraceae, Cucurbitaceae, Rutaceae, Lamiaceae, Amaranthaceae, Malvaceae, Solanaceae, Phyllanthaceae, Euphobiaceae, Vitaceae, and Anacardiaceae account for the 19 plant families that have consistently been identified as the most important from an ethnomedicinal perspective, are commonly used and have an important on pharmacological research in Thailand and Southeast Asia (Phumthum et al., 2019). That data concurs with Gonçalves et al. (2020), who identified aromatic plant families such as Myrtaceae, Rutaceae, Zingiberaceae, Lamiaceae, and Apiaceae. These plants possess biological characteristics that may prevent or treat neurological disorders due to their capacity to regulate diverse central nervous system cellular processes.

The previously mentioned compilation of plants has the purpose of supporting applications for authorization to manufacture, import, or distribute dietary supplements that contain medicinal plants (Food and Drug Administration, 2019). This is consistent with the study's aim to locate the plants that grow in Thailand so that the extracts derived from them can be ensured for use in the subsequent testing phase for the feasibility of functional food, neuroprotective, and antioxidant properties.

Analysis of antioxidant and neuroprotective capabilities has shown that 116 out of 153 medicinal plants in Thailand have these qualities by inhibiting the acetylcholinesterase enzyme. Additionally, the study found two medicinal plants, *Amorphophallus brevispathus,* which are endemic to Thailand and are found in the rhizomes and petals of *Rosa spp.* and hybrids, have never before been demonstrated to exhibit antioxidant properties. Tantaisong et al. (2023) investigated the antioxidant activity of *Amorphophallus brevispathus* in the prior study. The results of the study, however, were based on an antioxidant activity test of the leaves, which is not a component of an FDA-approved dietary supplement.

In addition, based on the systematic review of three Brazilian medicinal plants commonly consumed locally and therapeutic for various medicinal conditions. The plant’s antioxidant capability differs depending on which portion of the plant is used, ranging from very strong to moderate (Jacob et al., 2022). This is because each type of plant has unique therapeutic properties based on the components found in each part of the plant. For instance, common plant parts that contain alkalies are roots, leaves, bark, and seeds. Additional, frequent plant parts that contain essential oils are camphor wood,

clove buds, cinnamon bark, lemongrass leaves, and nutmeg seeds (Bhat, 2021). Consequently, the plants used in the FDA reports have been established to constitute the framework for this study and found that the part used by fifteen medicinal plants that were previously used in previous reports did not match.

The data collection results showed that ABTS showed more effective antioxidant activity in almost 50% of all plants than DPPH with very strong IC_{50} values of 39.66% and 31.90%, respectively (Table 3.1). This is consistent with previous studies that compared and examined the correlation between the two methodologies and found that the ABTS approach significantly outperforms the DPPH assay when evaluating antioxidant activity in various varieties of food (Floegel et al., 2011). Consequently, this study investigated the antioxidant activity correlation between ABTS and DPPH to determine the association between the antioxidant activity of all plants discovered in Thailand.

The antioxidant activity data of 116 medicinal plants discovered in Thailand were systematically reviewed, and the results showed a significant positive correlation ($r = 0.993$, $p<0.001$) between DPPH and ABTS. When compared to the correlation of antioxidant activity of 30 plant extracts from the study by Dudonné et al. (2009), who also tested using the Pearson correlation method, they found that the correlation of antioxidant activity between DPPH and ABTS with $r = 0.906$, which is less of a correlation than the results of the above study. This is consistent with a previous study that determined the antioxidant properties of 33 local Thai vegetable extracts using ABTS, DPPH, FRAP, and Folin-Ciocalteu reducing capacity assays to assess as well as analyze the correlations between antioxidant activity in each technique. The four test's antioxidant activity was shown to be strongly correlation ($r > 0.98$) (Prommajak et al., 2015). *Apium graveolens*, *Mangifera indica*, *Melissa officinalis*, *Morinda citrifolia*, *Moringa oleifera*, *Ocimum gratissimum*, *Piper sarmentosum,* and *Polygonum odoratum* are the species that have been investigated in this case and these are the same medicinal plants that the FDA has approved for use as dietary supplements. Reporting on the correlation between DPPH and ABTS for the antioxidant activity of the 50 most popular foods in the US with high antioxidant activity, according to the DPPH and ABTS assessments, there was a significant positive correlation between the antioxidant activity of the 18 fruits, 13 vegetables, and 19 beverages ($r = 0.949$, $p<0.001$) (Floegel

et al., 2011). This is thought to be consistent with the study's findings in this research. This is because the fruits, vegetables, and beverages including apples, avocado, banana, cherries, cranberry, grapes, lemons, oranges, pears, plums, strawberries, beans, cabbage, onion, pepper, and green tea that were included in the study also correspond to the list of medicinal plants that the FDA approved for use in the dietary supplement. It additionally offers substantial support for the study's findings.

The FDA has approved several plants for use in dietary supplements. Among medicinal plants include *Curcuma longa* (Borra et al., 2013), *Ananas comosus* (Fidrianny et al., 2018), *Illicium verum* (Rao et al., 2012), *Terminalia chebula* (Sasidharan et al., 2012), and *Zingiber officinale* (Ali et al., 2018), which has strong antioxidant properties, included previous studies have revealed the role of antioxidants in effectively preventing neurological disorders (Zafrilla et al., 2009). Because of this, studies on the neuroprotective properties of medicinal plants that have undergone an extensive systematic review and screening for antioxidant activity will continue. To ensure that the outcomes correspond with the aim of this study, which is to investigate the neuroprotective effects of medicinal plants that the FDA has approved for use as dietary supplements.

Numerous Thai medicinal plants that the FDA approved for use as dietary supplements have not been examined for their capacity to inhibit AChE, based on the result of a study on the enzyme's inhibitory activity. According to the findings of the aforementioned comprehensive study, it is therefore impossible to determine the effectiveness of such medicinal plants, including their ability to suppress the acetylcholinesterase enzyme. Comparing this study to the previous study conducted by Mukherjee et al. (2007), it was discovered that out of 50 plants known to inhibit AChE, such as *Aegle marmelos, Bacopa monniera, Carthamus tinctorius, Musa sapientum,* and *Piper nigrum*, only five medicinal plants were found in Thailand and FDA-approved matches. In addition, Ingkaninan et al. (2003), investigated the potential use of 32 Thai herbal extracts as medications for the treatment of AD by an examination of their AChE inhibitory effectiveness. Thai medicinal plants offer good AChE inhibitory effects, according to the study's findings. *Stephania suberosa* and *Tabernaemontana divaricata* are plants that have more than 90% AChE inhibition effectiveness. *Piper interruptum, Butea superba, Piper nigrum, Cassia fistula,* and *Piper interruptum* are

plants that have between 50 and 65% AChE inhibition ability. The rest plants have less than 50% AChE inhibition effect. Furthermore, research was conducted on the AChE inhibitory effects of Korean medicinal herbs, which are widely used to enhance memory and cognitive in the elderly. The results showed that at 200 µg/mL, extracts from Acorus calamus and Epimedium koreanum significantly inhibited enzyme activity (Oh et al., 2004).

Inhibition of AChE is one strategy that has been established to be effective for neuroprotection. The enzyme AChE is an essential enzyme that quickly hydrolyzes acetylcholine (ACh) to stop nerve impulse transmission at the cholinergic synapse (Schulz, 2003; Mukherjee et al., 2007). This neurotransmitter is involved in learning, memory, focus, attentiveness, and involuntary muscle action. This neurotransmitter is responsible for sending signals, or stimulation, from the brain to many parts of the body (Suryanarayanan, 2014). In numerous taxonomic groups across the plant world, ACh is present. The chlorine acetyltransferase (CHAT) activity is present in certain plants. With the help of precursors like choline and acetyl coenzyme, this enzyme can produce ACh. Many tissues of plants also contain AChE activity. Plants appear to metabolize Ach based on the presence of both CHAT and AChE in their tissues (Tretyn & Kendrick, 1991). According to the previously mentioned fact that plants are the natural source of AChE inhibitors, the study on the AChE inhibitory effects of plants has drawn an abundance of attention for it to be useful as a therapeutic guide for neurological disorders.

Currently, neurological diseases like AD are treated with medications that inhibit AChE. This medicine, rivastigmine, a semi-synthetic derivative of physostigmine, is derived from plant extracts and is used to treat the symptomatic treatment of patients with mild to moderate AD. The alkaloid physostigmine is present in the manchineel tree (*Genus hippomane*) and calabar bean (*Physostigma venenosum*) (Howes & Perry, 2011). In 2001, the FDA approved galantamine for the treatment of mild to moderate AD (Thompson, 2001). Galantamine (found in *Lycoris radiata*) is an active natural alkaloid inhibiting the enzyme acetylcholinesterase in AD. (Kumar et al., 2017; Lilienfeld, 2002; Maelicke et al., 2009; Olin & Schneider, 2002). AChE inhibitors also have drawbacks, such as gastrointestinal difficulties and problems with bioavailability (Mukherjee et al., 2007). More than 90% of patients receiving

cholinesterase inhibitors reported digestive problems such as nausea and vomiting, according to a study comparing the drug's effectiveness in treating dementia in Alzheimer's patients to ginkgo extract (Schulz, 2003). To lessen these limitations, research has been done to identify natural extracts with superior AChE inhibitory properties that can lessen these restrictions.

This is consistent with the aim of this study, which is to improve the FDA-certified medicinal plant extracts for use as health foods that have been shown to have antioxidant and AChE inhibitory properties and are readily accessible and distributed at the level of the food industry. It decided to use these plant extracts in the next part of the *in vitro* study since the findings indicated that 21 medicinal plant extracts are commercially available.

Following a comprehensive review of the systematic review, 21 medicinal plant extracts from Thailand including commercially available medicinal plant extracts that the FDA had approved for use in dietary supplements with antioxidant and AChE inhibitory activities were examined to determine the total phenolic compounds, total flavonoid compounds, and free radical scavenging activities of the selected plant's parts. Most antioxidant activities in plants or plant-derived products are attributed to phenolic compounds, which comprise the largest phytochemicals (John et al., 2014; Phong et al., 2022). They do this by either preventing hydroperoxides from breaking down into free radicals or neutralizing free radicals in lipids (Maisuthisakul et al., 2007).

Spectrophotometric evaluations of the TPC and TFC were achieved using the Folin-Ciocalteu and aluminium chloride colorimetric methods, respectively. Because it is straightforward and repeatable for identifying and measuring phenolic and flavonoid compounds in a wide variety of food and biological samples. (Pérez et al., 2023). According to the Folin-Ciocalteu and aluminium chloride colorimetric methods, *Coffea arabica* from green coffee bean and *Curcuma longa* extracts had the highest TPC and TFC content of all the medicinal plant extracts evaluated. It was also significantly higher than that of the previous study by Kiattisin et al. (2016), which examined the antioxidant activity of two coffee species (Arabica and Robusta), both of which are economically important crops in Thailand and are widely cultivated in both the north and the south. The results showed that the TPC of green coffee beans extracted with

ethanol from Arabica had the highest TPC, while the TPC of roasted coffee beans was lower, at 255.99±2.05 and 90.95±1.93 mg gallic acid/ g of extract, respectively. More intensive roasting procedures result in a decrease in the amount of phenolic compounds in coffee beans (Wu et al., 2022). In addition, TPC and TFC evaluation findings showed that the contents of *Curcuma longa* were twice as high as those of three Indian curcuma species: *Curcuma longa*, *Curcuma caesia*, and *Curcuma aamda*. These species' average TPC and TFC values were 92.30±0.05 to 260.00±0.25 mg gallic acid/ g of extract and 22.52±0.02 to 79.36±0.01 mg quercetin/ g of extract (Sahu & Saxena, 2013). Although the test results indicated that *Curcuma longa* had the highest TPC and TFC contents, these values were lower than the present study's findings, which were 185.22±8.87 mg gallic acid/ g of extract and 514.13±50.55 mg of catechin/ g of extract, respectively.

Through the utilization of multiple antioxidant mechanisms, including MCA, DPPH, ABTS, FRAP, and NBT, the antioxidant properties of 21 medicinal plant extracts were examined to identify the medicinal plants that exhibited the highest percentage of inhibition on the biding of transition metals, inhibition of DPPH, ABTS, and superoxide anions, and the ability to reduce transition metals. The results of heatmap analysis demonstrated that only 6 medicinal plants were highly effective at inhibiting these free radicals and exhibited the same pattern of antioxidant activity including *Bacopa monnieri*, *Camellia sinensis*, *Coffes arabica*, *Curcuma longa*, *Tagetes erecta*, and *Terminalia chebula*. Heatmap visualization allows for rapid information summary with a third quantitative dimension represented by different colors and is a helpful screening tool for quickly testing broad ideas on the relationship between exposure measurements, biomarkers, metadata, or host parameters (Pleil et al., 2011). Some samples showed % inhibition values above 100%, likely due to factors like high antioxidant concentrations reducing radicals too much, interference from other sample components, or errors in measurements. To improve accuracy, future studies should adjust sample concentrations. Despite these issues, the results still suggest strong antioxidant activity, but improvements in the experimental setup are needed.

. Possible causes include over-reduction of radicals by highly concentrated antioxidants, interference from sample components, instrument-related errors, or data processing issues. To reso

Antioxidant capacity is studied by examining the process of free radical protection by evaluating the capacity to bind to transition metals, which are frequently present in the body as ferrous or ferric ions and are one of the causes that lead to the creation of free radicals. These are catalysts for the Fenton reaction, producing hydroxyl radicals that impact DNA damage or biomolecule destruction (Zheng et al., 2008). Antioxidants can attach directly to ferrous ions and stop oxidative stress-related damage. The extracts' capacity to bind to transition metals might be the result of their ability to accelerate in redox reactions, which involve metal ion binding. The higher concentrations of phenolics and flavonoids could be connected to the metal-chelating activity. Johr and Khan (2018) found that the n-butanol extract of *Piper betel* has a significant level of metal chelating activity (64.6% at a concentration of 3.2 mg/mL). Dihydroxyl groups that relate to transition metals and prevent metal-induced free radical scavenging may be present in the extract. The extract's chelating agents cause a red decrease by preventing the formation of ferrozine-Fe^{2+} complexes (Aboul-Enei et al., 2002). According to the study of transition metal biding ability, *Curcuma longa* exhibited the highest activity. This is probably due to its high TPC and TFC, which is consistent with the results.

In the DPPH and ABTS assays, *Coffea arabica*, *Curcuma longa,* and *Bacopa monnieri* had highest antioxidant activity with statistical significance at $p<0.05$ when the ability of medicinal plants to scavenge free radicals was investigated with electron transfer and hydrogen atoms (Mixed-mode based assay). The DPPH and ABTS assay are a popular technique for assessing the effectiveness of different antioxidants in scavenging free radicals in antioxidant activity testing. This is due to the method's simplicity, rapidity, sensitivity, high precision, and repeatability (Nguyen et al., 2021; Ozcelik et al., 2003). Furthermore, the antioxidant activity is measured using the same principle in both approaches, which also measure the transfer of electrons and hydrogen atoms as well as the reduced light absorption of free radical dyes. It tested the ability of biological samples to eliminate or reduce free radicals to cause the color of the radicals to decrease autonomy using the artificially generated and physiologically unrelated free

radicals, DPPH and ABTS, which have synthetic colors of purple and green, respectively (Ak & Gülcin, 2008; Bibi Sadeer et al., 2020; Floegel et al., 2011; Huang et al., 2005). The ABTS assay effectively evaluates antioxidant capacity better than the DPPH assay. DPPH is a synthetic free radical that has a readily soluble molecular structure in fat (Hydrophobic), making it a good fit for non-polar antioxidants. Because ABTS is a free radical with a molecular structure that is soluble in water and fat (Hydrophilic), antioxidants with both polar and non-polar characteristics can be studied using the ABTS assay. Consequently, the antioxidant capacity of the antioxidant samples could be tested using the ABTS assay, which is more diverse than the DPPH assay (Floegel et al., 2011), this is also consistent with the results in this study.

However, when investigated with the NBT method under normal superoxide anion radical conditions, *Tagetes erecta*, *Camellia sinensis*, and *Terminalia chebula* showed the top three best activity, according to the study of superoxide anion antioxidant capacity. Superoxide anion is one of organisms' most relevant and physiologically important ROS free radicals. It continually produces in cells. It is a precursor to other free radicals that contain oxygen (Xu et al., 2013). Increasing ROS concentrations may significantly mediate oxidative stress, which damages lipids, cell membranes, proteins, and DNA, among other biological components. The harmful consequences of oxidation-induced ROS develop in throughout an individual's life and age-related illnesses like cancer, atherosclerosis, arthritis, neurological diseases, and other diseases are largely caused by them (Valko et al., 2006). According to a study by Siddhu and Saxena (2017), which evaluated the antioxidant capacities of *Tagetes erecta* flower extracts in four different solvents, the methanol extract was most successful at scavenging superoxide free radicals, with an IC_{50} value of 64.22±0.04 µg/mL, this extract is thought to be the most effective superoxide radicals scavenger. It was comparable to the ethanol extract in this study, which had an IC_{50} value of 0.06±0.01 mg/mL.

The study on antioxidant activity using various techniques showed that *Curcuma longa* is a medicinal plant with excellent antioxidant capacity with mechanisms for protecting against free radicals when tested by transition metal biding ability analysis, good antioxidant activity with mechanisms for transferring electrons and hydrogen atoms when tested by DPPH and ABTS assays, and antioxidant activity

with mechanisms for single transferring electrons when tested by FRAP assay. *Curcuma longa* has been the subject of numerous studies exploring its potential as a treatment for various diseases, including cancer, cardiovascular disease, obesity, liver disease, inflammatory disease, aging, and neurodegenerative diseases (Monroy et al., 2013).

Excessive Curcuma longa intake may trigger uterine contractions during pregnancy and impair iron absorption, posing risks for iron-deficient individuals. It has been reported to lower testosterone levels and reduce sperm motility in men when consumed orally. Additionally, Curcuma longa can delay blood clotting, necessitating its discontinuation at least 2 weeks before surgery. People with gallbladder disease or bleeding disorders should avoid its consumption (Fuloria et al., 2022). Curcumin has a well-established safety record, with an allowable daily intake of 0-3 mg/kg body weight, as recognized by the Joint United Nations and World Health Organization Expert Committee on Food Additives (JECFA) and European Food Safety Authority (EFSA). Clinical trials on healthy individuals support its safety and efficacy (Hewlings & Kalman, 2017). However, some side effects have been reported, including high doses of diarrhea, headache, rash, and yellow stool (500-12,000 mg) (Lao et al., 2006). Long-term intake (0.45-3.60 g/day for 1-4 months) has also been linked to nausea, diarrhea, and elevated liver enzymes (Marchiani et al., 2014).

While investigating previous studies on *Curcuma longa*'s antioxidant properties, it was found to have a significant amount of TPC and TFC, with 15.53±0.53 mg gallic acid/ g of extract and 13.67±1.63 mg quercetin/ g of extract, respectively. Additionally, *Curcuma longa* demonstrated high free radical scavenging capacities at varied concentrations (500, 250, 100, 50, and 25 µg/mL) when tested with the DPPH method; the resulting IC_{50} values were 83.89%, 73.54%, 38.92%, 24.55%, and 18.69%, respectively (Rahul et al., 2022). Following the study findings by Priyanka et al. (2017), methanol extracts of eight Indian turmeric cultivars demonstrated strong DPPH free radical scavenging properties with %inhibition values ranging from 49.63±2.97 to 59.58±2.82 µg/mL. Apart from its antioxidant properties, curcumin, one of the three curcuminoids found in *Curcuma longa*, gas present anti-inflammatory, antispasmodic, anti-angiogenic, and anti-cancer properties in several *in vitro* and *in vivo* studies by blocking growth factor receptor activity (Alabdali et al., 2021). Curcumin, DMC, and

Bis-DMC are the three curcuminoid chemical compounds that may be separated using column chromatography and identified using spectroscopy (Jayaprakasha et al., 2002).

Several components, particularly the three curcuminoid compounds, could be isolated, with distinct peaks of curcumin and its derivatives, according to an analysis of the chemical composition and derivatives in the *Curcuma longa* extract. The *Curcuma longa* extract contained 69.83 mg/kg of curcumin, DMC, and Bis-DMC, in that order. According to the study by Abualhasan et al. (2023), which used a gas chromatography-mass spectrometer (GC-MS) and HPLC techniques to characterize the composition of *Curcuma longa* extracts, the primary component, curcumin was separated along with two additional curcumin derivatives. Consistent with the study of Opustilová et al. (2023), curcumin was evaluated by HPLC analysis, which showed three peaks. Curcumin was the primary peak, with DMC, and Bis-DMC presenting as minor peaks close to the main peak.

On the other hand, *Curcuma longa*'s chemical characteristics concerning absorption are limited. Previous studies on the pharmacokinetics of curcumin have demonstrated the absorption properties of curcuminoids. it has been discovered to be metabolized in the gastrointestinal and to be poorly absorbed orally in the gastrointestinal tract (Ammon & Wahl, 1991; Ravindranath & Chandrakhara, 1980; Sharma et al., 2001). Due to its poor solubility, rapid metabolism, and poor pharmacokinetic profile, curcumin has poor oral absorption, resulting in low plasma and tissue levels in addition to limited effectiveness when consumed (Anand et al., 2007; Kurita & Makino, 2013). Since curcumin has limitations, researchers are interested in reducing these limitations by developing a microencapsulated form of *Curcuma longa* extract.

According to studies on the results of developing microencapsules from *Curcuma longa* extract using the spray drying technique, which is an appreciated and very effective technology for encapsulating bioactive compounds from plant extracts (Dewi et al., 2023), one of the primary considerations when selecting a material for production is the wall material that covers the core material because it has the potential to oxidize the core material through the microcapsule's surface or structure. Maltodextrin and gum Arabic have been studied to support their good encapsulation efficiency, which is why the researcher gathered them as wall materials to coat the

Curcuma longa extract in this study. The study of Çam et al. (2014), used maltodextrin as the encapsulating agent and pomegranate peel extract (*Punica granatum*) as the core material. At 160°C as the entry temperature, the core-to-encapsulated ratios were 1:1 and 1:3. Microencapsulation efficiency ranged from 97.9% to 98.4%, according to the various ratios (10:0, 8:2, and 6:4) for coating. To investigate the encapsulation efficiency, morphological characteristics, total phenolic compounds, and antioxidant activity, the red grape extract was encapsulated at ratios of 1:1 and 1:2 at inlet temperatures of 120, 140, 160, and 180°C. The microcapsules coated with maltodextrin and gum Arabic at a ratio of 8:2 at an inlet temperature of 140°C were found to have the highest efficiency and the best values of all experimental parameters, the greatest results with strong antioxidant activity, TPC, and moisture absorption capacity (Tolun et al., 2016). In addition, curcumin microencapsulation was shown to have a strong water solubility ranging from 78.42% to 87.27%, which makes it more soluble in water than the un-microencapsulated *Curcuma longa* extract. Sapariya et al. (2023) found that WSI of the extract for, the rhizomes of *Curcuma longa* was only 16.17% to 26.51%. Nevertheless, utilizing porous starch and gelatin as wall materials, the study found that the free curcumin was insoluble in water at room temperature when it was microencapsulated using spray drying. The solubility significantly enhanced when the powder was instantly dissolved after 2 minutes of being powdered following the spray drying procedure (Wang et al., 2009).

Despite their distinct antioxidant methods, the six curcumin microencapsule formulations exhibited comparable antioxidant efficacy. More specifically, curcumin microencapsules coated with a 1:10 ratio of maltodextrin and gum Arabic (sCL11010, sCL11082, and sCL11064) showed superior antioxidant activity compared to formulations with a 1:20 wall material ratio (sCL12010, sCL12082, and sCL12064). Compared to the unmicroencapsulated *Curcuma longa* extract, sCL11064 with a coating ratio of maltodextrin and gum Arabic at a 6:4 ratio showed high antioxidant activity on par with. Following the study of the stability improvement of anthocyanin from roselle (*Hibiscus sabdariffa*) using the spray drying method, which used maltodextrin as wall material mixed with core material at three different ratios (30:70, 40:60, and 50:50), the most appropriate ratios were determined to be 50:50. With a yield of 73.60%, spray drying significantly outperformed other formulas ($p<0.05$). the

powder had an average particle size of 4.48 µm, was widely distributed, had a moisture content of 2.5%, and showed DPPH antioxidant activity with an IC_{50} value of 3.40 mg/mL (Millinia et al., 2024). Furthermore, microencapsules produced from *Moringa oleifera* leaf extract at an inlet temperature of 180°C and a maltodextrin wall-to-core ratio of 10:1 demonstrated the highest ABTS radical scavenging activity (SC_{50} 2.71±0.03 mg/mL). The microcapsules TPC and TFC were 3.95±0.21 mg gallic acid/ g of extract and 3.06±0.28 mg catechin/ g of extract, respectively (Vonghirundecha et al., 2022). Additionally, with microencapsulated sCL11064 having a strong antioxidant capacity, the active constituents of the microencapsulated formula were evaluated, and the results suggested a statistically significant ($p<0.05$) high content of total phenolic and flavonoids. Three curcuminoid compounds: curcumin, DMC, and Bis-DMC were identified, which agreed with those found in the previously issued *Curcuma longa* extract utilizing HPLC techniques.

Because curcumin is a potent antioxidant, it can potentially decrease the damage that the body's biological processes such as respiration, digestion, hormone synthesis, and symbiotic metabolism cause to cells, particularly mitochondrial damage (Xu et al., 2023). Through redox signaling, it can generate oxidants, such as superoxide radicals ($O^{2\bullet-}$), hydroxyl radicals ($^{\bullet}OH$), and hydrogen peroxide (H_2O_2), which are all the consequences of molecular oxygen reduction (Antunes & Brito, 2017). Excessive accumulation of free radicals in the body can lead to cell death, affect the development of diseases, and reduce an organism's lifespan (Shailaja et al., 2017). As *C. elegans* lifespan is short and reproducible, it is an ideal model organism for research on aging. Its whole genome has been sequenced, and most signaling pathways are compatible with evolution (Palikaras et al., 2015). It was therefore employed in this lifespan study.

Based on the evaluation of the most appropriate concentration of sCL11064 for extending the lifespan of *C. elegans* using the food clearance method. It was found that the food intake of *C. elegans* receiving sCL11064 at concentrations of 100 to 1,000 µg/mL was not significantly different ($p<0.05$) compared to the control group. The food clearance method efficiently tests the extract's toxicity and identifies the range of concentrations of the compound to be tested in *C. elegans*. It analyzes the change in the optical density of bacteria by measuring the rate at which *C. elegans* intakes *E. coli.* Because the food clearance assay depends on *C. elegans* at the larval stage (L1), it

typically takes three days for the organism to mature into adulthood. Therefore, if the extract is not toxic to growth, food intake, and reproduction that will result in offspring, the rate of food elimination will decrease after the third day (Ullah et al., 2024; Voisine et al., 2007). The results suggested that sCL11064 did not affect *C. elegans* growth, survival, or reproduction at every concentration. As with the examination of *C. elegans*' pharyngeal pumping rate after receiving sCL11064 at concentrations ranging from 100 to 1,000 µg/mL, there was no significant difference ($p<0.05$) compared to the control group. It is important to comprehend feeding behavior because poor feeding behavior can lead to increased health risks and associated diseases. The pharyngeal movements used by *C. elegans* to feed are pumping and peristalsis. The pharyngeal organ, a neuromuscular sucking organ, is a great model for researching feeding behavior as it is transparent and has a distinctive cellular structure that makes it easy to identify under a microscope. By increasing the sensory perception and subsequent neural transmission from the outside, *C. elegans*' feeding activity demonstrates the ability to eliminate microorganisms, which aids in determining the toxicity of extracts or medications (Calahorro et al., 2021; Shanmugam & Kapahi, 2024; Scholz et al., 2016; Scholz et al., 2017; Trojanowski et al., 2016).

According to the survival rate study of *C. elegans* under oxidative stress induced by paraquat at a concentration of 50 mM, sCL11064 at a concentration of 100 to 1,000 µg/mL was able to considerably increase the lifespan of *C. elegans* ($p<0.05$) in comparison to the control group. The herbicide paraquat is an organic substance that generates hazardous oxygen molecular and free radical ROS, which are superoxide anions that can damage cell components and are a primary cause of accelerated aging as well as reduced lifespans (Castello et al., 2007; Park et al., 2017; Senchuk et al., 2017; Van Raamsdonk & Hekimi, 2012). Survival rate studies conducted under oxidative stress conditions can show how effectively biological remediation responds to oxidative stress. In the study by Hwang et al. (2014), *C. elegans*' lifespan was shortened when exposed to high concentrations of paraquat because it caused acute oxidative stress, which led to the organism's rapid death. Based on the results, sCL11064 may eliminate superoxide anions, increasing the *C. elegans* average lifespan. In a study of antioxidant activity and lifespan extension of Quercetin-3-O-α-L-rhamnopyranosyl(1→2)-O-α-L-rhamnopyranoside (QDR) using a *C. elegans* model

system, it was found that the DPPH radical scavenging activity of QDR was as potent as vitamin C and that it effectively extended the lifespan of *C. elegans* under both normal culture conditions and oxidative stress induced by 80 mM paraquat. The worms lived 15.5% longer than the control group (Ahn et al., 2014). Based on the study's results, *C. elegans* is not significantly toxically affected by concentrations of 100, 250, 500 µg/mL ($p<0.05$), determined by the survival rate test following paraquat induction and the lifespan extension analysis following sCL11064 treatment. In this study, the concentration of 1,000 µg/mL sCL1106 showed no significant effect on the mean lifespan of *C. elegans* compared to lower concentrations (100, 250, and 500 µg/mL). This may be due to a saturation point where higher curcumin levels do not further improve lifespan, or potentially because high concentrations could cause toxicity or disrupt normal processes. The bioavailability of curcumin and its release from microencapsulation might also limit the effectiveness at higher doses. Further research is needed to determine the optimal concentration for promoting longevity and to explore the mechanisms involved. As a consequence, the researchers chose these concentrations for investigating the neuroprotective properties of sCL11064 in *C. elegans*. It wanted to know if sCL11064 at 100, 250, and 500 µg/mL had potential neuroprotective effects.

Neuroprotective effect of curcumin microencapsulated in the *C. elegans* model; this study tested the protective effect of DA neurons against 6-OHDA-induced neurodegeneration using the PD model of *C. elegans* in the BZ555 strain. The results demonstrated that *C. elegans* exposed to 50 mM 6-OHDA exhibited a PD-like phenotype, and that treatment with sCL11064 at 100, 250, and 500 µg/L had no significant effect on the fluorescence expression of the dopamine transporter marker P*dat-1*:GFP in ADE and CEP neurons. In *C. elegans*, there are eight DA: two anterior deirid (ADE) neurons, which are two pairs of mechanosensory neurons on the head; four cephalic (CEP) neurons, which are four pairs of mechanosensory neurons on the head that extend to the nose; and two posterior deirid (PDE) neurons, which are two pairs of neurons with cilia on the worm's dorsal side (Chou et al., 2022; McMillen &Chew, 2023). DA in the *C. elegans* transgenic strain BZ555 consistently expresses GFP, and the intensity of GFP fluorescence signifies the viability of the neurons (Kamireddy et al., 2018; Li et al., 2016). To induce DA degeneration in *C. elegans*, this study used 6-OHDA, a classical neurotoxin related to dopamine that has been

demonstrated to cause PD-like symptoms in experimental animals. DA transporters especially absorb 6-OHDA into DA neurons, by inhibiting complex I of the respiratory chain, it causes oxidative stress. 6-OHDA causes DA neurons in *C. elegans* to gradually deteriorate or die (Nass et al., 2002; Offenburger et al., 2018; Schober, 2004).

The fluorescence expression of the DA transporter marker P*dat-1*:GFP was examined in the ADE and CEP location in this study because previous study has demonstrated that 6-OHDA exposure significantly decreases GFP fluorescence in ADE and CEP neurons and marginally decreases it in other *C. elegans* DA (Li et al., 2016). The results of this study showed that sCL11064 is unable to inhibit the neurodegeneration induced by 6-OHDA. It is possible that the sCL11064 used in the test was too low a concentration, which could have produced the expression of a neurodegeneration inhibitory effect comparable to the control group. In contrast to the previous study that examined the effectiveness of the Chinese herbal plant *Astragalus mongholicus,* which the plant can inhibit the neurodegeneration induced by 6-OHDA at concentrations ranging from 1 to 4 mg/mL (Li et al., 2016). The study by Malaiwong et al. (2019), that the effects of *Holothuria leucospilota* extract in *C. elegans* BZ555 strains that caused neurodegeneration with 6-OHDA were investigated. Tested at concentrations ranging from 100 to 500 µg/mL, it was discovered that the extract had a good anti-PD effect in a PD model caused by 6-OHDA poisoning. It's conceivable that the curcumin microencapsulated in this study included just 10% of the *Curcuma longa* extract, which might not have demonstrated any inhibitory effect on 6-OHDA-induced neurological damage, which is why sCL11064 demonstrated no neuroprotective effects in C. *elegans*. In the future, more research might be conducted by adjusting the *Curcuma longa* extract to have larger volumes in the microencapsulation to improve the neuroprotective activity.

Following the feasibility study of using microencapsules as functional ingredients in the food industry using extruded ready-to-eat snacks as a food model, curcumin microencapsulated sCL11064 which received approval from the FDA's medicinal plant list has a high antioxidant capacity, a significant neuroprotective efficiency, the potential to be developed into a portion of functional food, and a high level of consumer acceptance. In recent years, there has been a significant global increase in the demand for healthy food and beverages, especially those that support

health and prevent disease. It follows that plant-based health components are widely used due to their beneficial phytochemical properties (Intrasook et al., 2024; Nazir et al., 2019).

Curcumin microencapsules sCL11064 are developed as functional foods using extrusion technology because of their high production capacity, continuous operation, high yield, flexibility, low cost, and wide application in the food industry (Alam et al., 2015). High-temperature short-time (HTST) a high-pressure, high-temperature extrusion process decreases microbial contamination and inactivates enzymes (Bayomy et al., 2024; Bordoloi & Ganguly, 2014). Because extruded products are injurious and without nutrients such as high calories, low protein, and minerals as well as containing less bioactive compounds, they are frequently referred to as junk food (Korkerd et al., 2015; Neder Suárez et al., 2021). As a result, local rice flour and unripe banana flour are naturally gluten-free and have been shown to have effective oil absorption, high solubility, and high swelling power (Kunyanee et al., 2024; Park & Kim, 2023), this strategy was selected to develop sCL11064 as functional foods in this study.

Extruded snacks prepared from flour enhanced with sCL11064 had no energy from fat and high levels of total energy, carbohydrate, protein, sodium, calcium, iron, and fiber, according to the nutritional value analysis. Furthermore, the product accepted high consumer approval (7.2-8.0) with statistical significance ($p<0.05$). Based on the sensory evaluation of 100 participants, the HFCb group significantly exceeded the RFCb group concerning acceptance and interest in the product. Similar to the development of extruded snacks including defatted soybean meal and germinated brown rice meal, which demonstrated high customer acceptability ratings (5.43-6.13). The findings suggest that products made from waste materials can be used successfully as snacks with higher nutrients (Korkerd et al., 2015). Furthermore, the HFCb group received 43.10 points on the willingness to recommend or mention to friends extruded snacks prepared from flour enriched with sCL11064, indicating they are impressed and want to spread the word about it. The RFCb group, on the other hand, scores -36.27 on a willingness to tell or recommend to friend scale. This suggests that while the HFCb group supports the extruded snack product derived from flour enriched with sCL11064, the RFCb group is not very interested in it. Therefore, the ability of this study to develop an extruded snack product containing flour enhanced with sCL11064, which has strong

antioxidant and neuroprotective properties, that is accessible to all consumer groups or the general public is still a limitation.

5.2 Conclusion

In conclusion, the 211 medicinal plants that have been accepted by the Food and Drug Administration (FDA) for use as dietary supplements have been investigated for their antioxidant capacity and fundamental mechanisms associated to their neuroprotective effects. A systematic review of the literature, including *in vitro* antioxidant activity testing, has shown that *Curcuma longa*, a medicinal plant is cultivated locally, has good antioxidant capacity, and a good neuroprotective effect. *Curcuma longa* has been processed into microencapsules to improve its solubility and absorption efficiency. sCL11064, the best effective curcumin microencapsules in terms of antioxidant activity, was tested on *in vivo* study using *C. elegans*. It found that sCL11064 did not cause toxicity to *C. elegans* in the experimental *in vivo* test based on feeding behavior test. It additionally demonstrated a high survival rate under conditions of paraquat-induced oxidation, which increased the lifespan of *C. elegans*. Additionally, it had neuroprotective effects against neurodegeneration in DA neurons induced by 6-OHDA, although there are still limitations in concentrations that have not yet produced positive results. Furthermore, curcumin microencapsulated sCL11064 can be applied as a functional ingredient in the food industry as extruded, ready-to-eat snacks, which have been accepted by consumers.

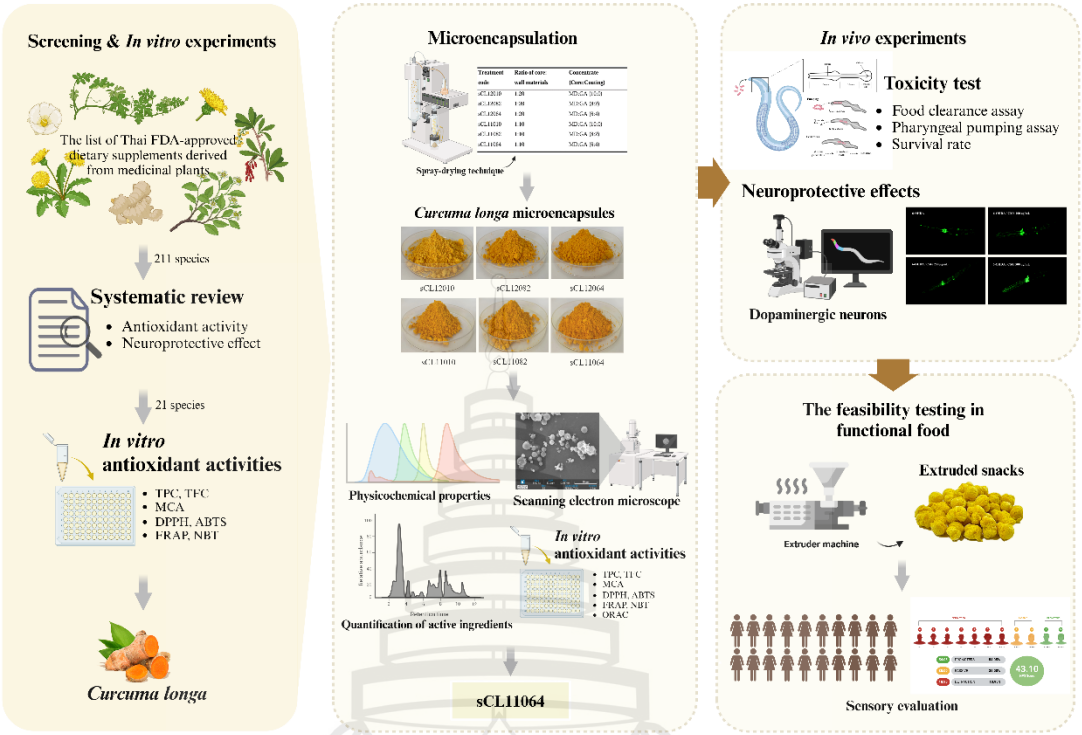


Figure 5.1 Graphical conclusion

5.3 Limitations

5.3.1 Pharmacokinetic Test

The solubility of curcumin microencapsules has been examined, but the body's ability to absorb them has not. Therefore, to determine whether curcumin microencapsules can be absorbed efficiently or not, the pharmacokinetic test should be used to determine the efficiency of absorption into the body.

5.3.2 Neuroprotective Effect Test

This study solely examined PD because there are several neurodegenerative diseases that have a high incidence and have an important impact on the current disease burden. In order to verify the effectiveness of neuroprotection, it should be evaluated in order diseases, such Alzheimer's disease.

5.4 Suggestion for Future Research

5.4.1 Microencapsulation Stability

Future studies should prioritize optimizing encapsulation material, exploring novel techniques, refining the release control mechanism, and evaluating the impact of physiological and environmental factors on curcumin stability. To develop more effective curcumin microencapsulates with enhanced therapeutic potential across various applications.

5.4.2 *In vivo* study of the Antioxidant Effect

To determine which antioxidant effects, such as those of superoxide dismutase (SOD) activity, catalase (CAT) activity, and malondialdehyde (MDA) level, the body can inhibit, an antioxidant effect test should be carried out in experimental *in vivo* study.

5.4.3 Neuroprotective Effects Test in the Rodent Model

To ensure that the study is comprehensive, behavior, learning, and short- and long-term memory are all studied.

5.4.4 Clinical Study Neuroprotective Effect Test

Since the aim of the study is to delay the beginning of neurological disorders, this might be a long-term clinical test to determine whether the dietary supplement may delay the onset of neurological diseases.

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APPENDIX A

METHODOLOGY

Table A1 The list of Thai Food and Drug Administration (FDA) approved dietary supplements obtained from medicinal plants

No	Scientific name	Common name	Family	Part used	Imported herbs
1	*Actinidia arguta* (Siebold & Zucc.) Planch. ex Miq.	Arguta kiwifruit	Actinidiaceae	Fruit	√
2	*Actinidia chinensis* Planch.	Kiwifruit	Actinidiaceae	Fruit	X
3	*Aegle marmelos* (L.) Corrêa	Bael fruit	Rutaceae	Ripe fruit	X
4	*Allium cepa* L.	Onion	Amaryllidaceae	Rhizome	X
5	*Allium fistulosum* L.	Onion	Amaryllidaceae	Leaf/ Stem	X
6	*Allium sativum* L.	Garlic	Amaryllidaceae	Rhizome	X
7	*Allium schoenoprasum* L.	Chives	Amaryllidaceae	Rhizome	X
8	*Aloe vera* (L.) Burm.f.	Aloe	Asphodelaceae	Gel	X
9	*Alpinia galanga* (L.) Willd.	Galangal	Zingiberaceae	Rhizome	X
10	*Amorphophallus brevispathus* Gagnep.	NA	Araceae	Rhizome	X
11	*Ananas comosus* (L.) Merr.	Pineapple	Bromeliaceae	Fruit	X
12	*Angelica polymorpha* Maxim.	Dong quai	Apiaceae	Root	X
13	*Antidesma ghaesembilla* Gaertn.	Mamao	Phyllanthaceae	Fruit	X
14	*Apium graveolens* L.	Celery	Apiaceae	Leaf/ Stem	X
15	*Arctium lappa* L.	Burdock	Asteraceae	Root	X
16	*Aristotelia chilensis* (Molina) Stuntz	Maqui berry	Elaeocarpaceae	Fruit	√
17	*Aronia melanocarpa* (Michx.) Elliott	Aronia berry	Rosaceae	Fruit	√

Table A1 (continued)

No	Scientific name	Common name	Family	Part used	Imported herbs
18	*Arthrospira maxima* Setchell & Gardner (AHN)	Spirulina	Phormidiaceae	Seaweed	√
19	*Arthrospira platensis* Gomont (AHN)	Spirulina	Phormidiaceae	Seaweed	√
20	*Ascophyllum nodosum*	Norwegian kelp	Fucaceae	Seaweed	√
21	*Asparagus officinalis* L.	Asparagus	Asparagaceae	Shoot/ Stem	X
22	*Astragalus propinquus* Schischkin	Astragalus/ Huang Qi	Fabaceae	Root	√
23	*Atractylodes macrocephala* Koidz.	White atractylodes	Asteraceae	Rhizome	√
24	*Auricularia auricular*-Judae	Ear of rock	Auriculariaceae	Mushroom	X
25	*Avena sativa* L.	Oat	Poaceae	Seed	√
26	*Bacopa monnieri* (L.) Wettst.	Brahmi	Plantaginaceae	Whole tree	X
27	*Beta vulgaris* L. var. *conditiva*	Beetroot	Amaranthaceae	Root	X
28	*Boesenbergia rotunda* (L.) Mansf.	Finger root	Zingiberaceae	Rhizome/ Root	X
29	*Borago officinalis* L.	Borage	Boraginaceae	Seed	√
30	*Brassica oleracea* var. alboglabra (L.H.Bailey) Musil	Chinese broccoli	Brassicaceae	Leaf/ Stem	X
31	*Brassica oleracea italica x* alboglabra	Broccolini	Brassicaceae	Bloom/ Peduncle	√
32	*Brassica oleracea* L. var. *capitata* L.	Cabbage	Brassicaceae	Leaf/ Bloom	X
33	*Brassica oleracea* L. var. *italica* Plenck.	Broccoli	Brassicaceae	Bloom/ Stem/ Leaf	X
34	*Calendula officinalis* L.	Marigold	Asteraceae	Bloom	X
35	*Camellia sinensis* (L.) Kuntze	Green tea	Theaceae	Young shoots / Leaf/ Flower bud	X
36	*Canarium album* (Lour.) DC.	Chinese olive	Burseraceae	Fruit	X

Table A1 (continued)

No	Scientific name	Common name	Family	Part used	Imported herbs
37	*Capsicum annuum* L.	Chili/ Peppers	Solanaceae	Fruit	X
38	*Capsicum annuum* var.*grossum* (Willd.) Sendtn.	Peppers	Solanaceae	Fruit	X
39	*Capsicum frutescens* L.	Bird chili pepper	Solanaceae	Fruit	X
40	*Caralluma adscendens* var. fimbriata (Wall.) Gravely & Mayur.	NA	Apocynaceae	Aril	√
41	*Carica papaya* L.	Papaya	Caricaceae	Ripe fruit	X
42	*Carthamus tinctorius* L.	Safflower	Asteraceae	Bloom/ Seed	X
43	*Centella asiatica* (L.) Urb	Pennywort	Apiaceae	Leaf	X
44	*Chaenomeles speciosa* (Sweet) Nakai	Chinese quince	Rosaceae	Fruit	X
45	*Chlorella vulgaris* Beyerinck	Chlorella	Chlorellaceae	Seaweed	√
46	*Chrysanthemum indicum* L.	Chrysanthemum	Asteraceae	Bloom	X
47	*Chrysanthemum morifolium* Ramat.	Chrysanthemum	Asteraceae	Bloom	X
48	*Cichorium intybus* L.	Chicory	Asteraceae	Root	√
49	*Cinnamomum cassia* (L.) J. Presl	Cassia	Luaraceae	Bark	X
50	*Cinnamomum verum* J.Presl.	Cinnamon	Luaraceae	Bark	X
51	*Citrus aurantifolia* (Christm.) Swingle	Lime	Rutaceae	Fruit	X
52	*Citrus* x *aurantium* L.	Sour orange	Rutaceae	Fruit	X
53	*Citrus limon* (L.) Burm.f.	Lemon	Rutaceae	Fruit	X
54	*Citrus paradise* Macfad	Grapefruit	Rutaceae	Fruit	√
55	*Citrus reticulate* Blanco	Mandarin	Rutaceae	Fruit	X
56	*Citrus sinensis* (L.) Osbeck	Orange sweet	Rutaceae	Fruit	X

Table A1 (continued)

No	Scientific name	Common name	Family	Part used	Imported herbs
57	*Cladosiphon okamuranus*	Mozuku	Chordariaceae	Seaweed	√
58	*Cocos nucifera* L.	Coconut	Arecaceae	Fruit	X
59	*Codonopsis pilosula* (France) Nannf.	Radi Codonopsis	Campanulaceae	Root	√
60	*Coffea arabica* L.	Green coffee beans	Rubiaceae	Beans	X
61	*Coix lacryma-jobi* L.	Job's tears	Poaceae	Seed	X
62	*Cordyceps sinensis* (Berk.) Sacc.	Cordyceps	Clavicipitaceae	Whole tree	√
63	*Crataegus laevigata* (Poir.) DC.	Hawthorn	Rosaceae	Fruit	√
64	*Crataegus pinnatifida* Bunge	Hawthorn	Rosaceae	Fruit	√
65	*Cucumis melo* L.	Melon	Cucurbitaceae	Fruit	X
66	*Cucumis sativus* L.	Cucumber	Cucurbitaceae	Fruit	X
67	*Cucurbita pepo* supsp. *pep*	Pumpkin	Cucurbitaceae	Fruit/ Seed	X
68	*Curcuma longa* L.	Tumeric	Zingiberaceae	Rhizome	X
69	*Cymbopogon citratus* (DC.) stapf	Lemongrass	Poaceae	Stem	X
70	*Cynara scolymus* L.	Artichoke	Asteraceae	Leaf	X
71	*Daucus carota* L.	Carrot	Apiaceae	Root	X
72	*Dimocarpus longan* Lour.	Longan	Sapindaceae	Fruit	X
73	*Dioscorea polystachya* Turcz.	Chinese yam	Dioscoreaceae	Rhizome	√
74	*Dunaliella salina*	D salina	Dunaliellaceae	Seaweed	√
75	*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.	Siberian ginseng	Araliaceae	Root	√
76	*Equisetum arvense* L.	Horsetail	Equisetaceae	Stem	√
77	*Equisetum hyemale* L.	Horsetail	Equisetaceae	Stem	√
78	*Eucommia ulmoides* Oliv.	Du Zhong/ Hardy rubber tree	Eucommiaceae	Bark	√

Table A1 (continued)

No	Scientific name	Common name	Family	Part used	Imported herbs
79	*Euterpe oleracea* Mart.	Acai	Arecaceae	Fruit	√
80	*Fagopyrum esculentum* Moench	Buckwheat	Polygonaceae	Seed	√
81	*Fagopyrum tataricum* (L.) Gaertn	Tartary Buckwheat	Polygonaceae	Seed	√
82	*Foeniculum vulgare* Mill.	Fennel	Apiaceae	Seed	√
83	*Fragaria* x *ananassa* (Weston) Duchesne	Strawberry	Rosaceae	Fruit	X
84	*Ganoderma lucidum* (Curtis) P. Karst.	Reishi mushroom	Ganodermataceae	Mushroom	X
85	*Garcinia atroviridis* Griff. ex T.Anderson	Asam gelugor	Clusiaceae	Fruit	X
86	*Garcinia gummi-gutta* (L.) Roxb.	Gamboge	Clusiaceae	Fruit	X
87	*Garcinia mangostana* L.	Mangosteen	Clusiaceae	Fruit	X
88	*Ginkgo biloba* L.	Ginkgo	Ginkgoaceae	Leaf	X
89	*Glycine max* (L.) Merr.	Soybean	Fabaceae	Seed	X
90	*Glycyrrhiza glabra* L.	Liquorice	Fabaceae	Root	X
91	*Glycyrrhiza uralensis* Fisch.	Chinese Liquorice	Fabaceae	Root	X
92	*Grifola frondosa* (Dicks.) Gray	Maitake	Meripilaceae	Mushroom	X
93	*Gynostemma pentaphyllum* Thunb.) Makino	Jiao Gu Lan	Cucubitaceae	Leaf/ Stem	X
94	*Haematococcus Pluvialis*	NA	Hematococcaceae	Seaweed	√
95	*Helianthus annuus* L.	Sunflower	Asteraceae	Seed	X
96	*Helianthus tuberosus* L.	Jerusalem artichoke	Asteraceae	Rhizome	X
97	*Hericum erinaceus* (Bull.) Pers	Lion’s mane mushroom	Hericiaceae	Mushroom	X
98	*Hibiscus sabdariffa* L.	Roselle	Malvaceae	Sepal / Bloom	X
99	*Hippophae rhamnoides* L.	Sea buckthorn	Elaeagnaceae	Fruit	X

Table A1 (continued)

No	Scientific name	Common name	Family	Part used	Imported herbs
100	*Hordeum vulgare* L. Seed/ Endosperm	Barley	Poaceae	Young leaves/	X
101	*Houttuynia cordata* Thunb.	Plu kaow	Saururaceae	Leaf	X
102	*Illicium verum* Hook.f.	Star anise/ Chinese anise	Schisandraceae	Fruit	X
103	*Ipomoea aquatica* Forssk.	Water spinach	Convolvulaceae	Stem/ Leaf	X
104	*Kaempferia parviflora* wall.Ex Baker	Black galingale	Zingiberaceae	Rhizome	X
105	*Laminaria digitate*	Kelp/ Brown algae	Laminariaceae	Seaweed	√
106	*Laminaria japonica*	Japanese kelp/ Kombu/ Haidai	Laminariaceae	Seaweed	√
107	*Laminaria longicruris*	NA	Laminariaceae	Seaweed	√
108	*Laminaria sinclairii*	NA	Laminariaceae	Seaweed	√
109	*Lentinula edodes* (Berk.) Pegler	Shiitake	Marasmiaceae	Mushroom	X
110	*Linum usitatissimum* L.	Linseed/ Flaxseed	Linaceae	Seed	X
111	*Litchi chinensis* Sonn.	Litchi	Sapindaceae	Ariel	X
112	*Lithothamnion calcareum*	Red marine algae	Hapalidiaceae	-	√
113	*Lonicera japonica* Thunb.	Japanese honeysuckle	Caprifoliaceae	Bloom	X
114	*Lycium barbarum* L.	Goji berry	Solanaceae	Fruit	X
115	*Lycopersicon esculentum* Mill.	Tomato	Solanaceae	Fruit	X
116	*Malpighia glaba* L.	Barbadoscherry/ Acerola cherry	Malpighiaceae	Fruit	X
117	*Malus domestica* Borkh.	Apple	Rosaceae	Fruit	X
118	*Mangifera indica* L.	Mango	Anacardiaceae	Fruit	X
119	*Matricaria chamomilla* L.	Chamomile	Asteraceae	Bloom	X

Table A1 (continued)

No	Scientific name	Common name	Family	Part used	Imported herbs
120	*Medicago sativa* L.	Alfalfa	Fabaceae	Leaf/ Stem	X
121	*Melissa officinalis* L.	Balm	Lamiaceae	Leaf	X
122	*Mentha* x *piperita* L.	Peppermint	Lamiaceae	Stem/ Leaf	X
123	*Mentha spicata* L.	Spearmint	Lamiaceae	Leaf	X
124	*Momordica Cochinchinensis* (Lour.) Spreng.	Gac/ Spiny Bitter gourd	Cucurbitaceae	Fruit/ Seed coat	X
125	*Momordica grosvenorii* Swingle	Luo han guo	Cucurbitaceae	Fruit	X
126	*Morinda citrifolia* L.	Noni	Rubiaceae	Fruit/ Leaf	X
127	*Moringa oleifera* Lam.	Ben moringa/ Drumstick tree	Moringaceae	Young leaves	X
128	*Morus alba* L.	Mulberry	Moraceae	Leaf/ Fruit	X
129	*Musa sapientum* L.	Banana	Musaceae	Ripe fruit	X
130	*Myrciaria dubia* (Kunth) McVaugh	Rumberry/ Camu-camu	Myrtaceae	Fruit	X
131	*Ocimum basilicum* L.	Basil/ Sweet basil	Lamiaceae	Leaf/ Bloom	X
132	*Oenothera biennis* L.	Evening primrose	Onagraceae	Seed	X
133	*Olea europaea* L.	Table olive	Oleaceae	Fruit	X
134	*Ophiopogon japonicas* (Thunb.) Ker Gawl.	Lily turf	Asparagaceae	Root/ Fruit	√
135	*Opuntia ficus-indica* (L.) Mill.	Prickly pear	Cactaceae	Fruit/ Leaf/ Stem	X
136	*Opuntia robusta* J.C. Wendl.	NA	Cactaceae	Stem	X
137	*Origanum vulgare* L.	Oregano	Lamiaceae	Leaf	X
138	*Oryza sativa* L.	Rice	Poaceae	Seed/ Germ	X
139	*Paeonia lactiflora* Pall.	Chinese peony	Paeoniaceae	Root	X
140	*Palmaria palmata* L.	Dulse	Palmariaceae	Seaweed	√
141	*Panax ginseng* C.A. Mey.	Korea ginseng	Araliaceae	Root	√
142	*Panax notoginseng* (Burkill) F.H.Chen	Sanchi root	Araliaceae	Root	√

Table A1 (continued)

No	Scientific name	Common name	Family	Part used	Imported herbs
143	*Panax quinquefolius* L.	American ginseng	Araliaceae	Root	√
144	*Panicum miliaceum* L.	Millet	Poaceae	Seed	X
145	*Passiflora edulis* Sims.	Passion fruit	Passifloraceae	Fruit	X
146	*Perilla frutescens* (L.) Britton	Perilla	Lamiaceae	Seed	X
147	*Persea americana* Mill.	Avocado	Luaraceae	Fruit	X
148	*Petroselinum crispum* (Mill.) Fuss	Parsley	Apiaceae	Aril/ Leaf/ Seed Seed	X
149	*Phaseolus mungo* L.	Urd bean	Fabaceae	Seed	X
150	*Phaseolus vulgaris* L.	Bean	Fabaceae	Seed	X
151	*Phyllanthus emblica* L.	Indian gooseberry	Phyllanthaceae	Fruit	X
152	*Pinus massoniana* Lamb.	Pine	Pinaceae	Fruit	X
153	*Pinus pinaster* Aiton	Frenc maritime pine	Pinaceae	Bark	√
154	*Pinus strobus* L.	Pine bark	Pinaceae	Bark	√
155	*Piper nigrum* L.	Paper/ Black pepper	Piperaceae	Seed	X
156	*Piper sarmentosum* Roxb.	Wild betle leaf bush	Piperaceae	Leaf	X
157	*Pisum sativum* L.	Pea	Fabaceae	Pod/ Seed	X
158	*Plantago ovate* Forssk.	Psyllium seed	Plantaginaceae	Seed/ Seed coat	X
159	*Pleurotus ostreatus* (Jacq.) P. Kumm	Oyste mushroom	Pleurotaceae	Mushroom	X
160	*Plukenetia volubilis* L.	Sacha inchi/ Incapeanut	Euphobiaceae	Seed	X
161	*Polygonatum odoratum* (Mill.) Druce	Polygonatum	Asparagaceae	Rhizome	√
162	*Poria cocos* (Schw.) Wolf	Indian bread	Polyporaceae	Sclerotium / Root	√
163	*Prunus armeniaca* L.	Apricot	Rosaceae	Fruit	X

Table A1 (continued)

No	Scientific name	Common name	Family	Part used	Imported herbs
164	*Prunus cerasus* L.	Sour cherry/ Tart cherry/ Sweet cherry	Rosaceae	Fruit	X
165	*Prunus domestica* L.	Plum	Rosaceae	Fruit	X
166	*Prunus mume* (Siebold) Siebold & Zucc.	Japanese apricot	Rosaceae	Fruit	X
167	*Psidium guajava* L.	Guava	Myrtaceae	Fruit	X
168	*Pueraria lobate* (Willd.) Ohwi	Kudzu	Fabaceae	Root	√
169	*Punica granatum* L.	Pomegranate	Punicaceae	Seed/ Aril	X
170	*Pyrus arbustifolia* (L.) Pers	Aronia	Rosaceae	Fruit	√
171	*Rehmannia glutinosa* (Gaertn.) DC.	Rehmannia	Scrophularia Ceae	Root	√
172	*Ribes nigrum* L.	Blackcurrant/ Redcurrant	Grossulariaceae	Fruit/ Seed	√
173	*Rosa centifolia* L.	Rose	Rosaceae	Petal	X
174	*Rosa canina* L.	Rose hips	Rosaceae	Fruit	X
175	*Rosa spp.* and hybrid	Rose	Rosaceae	Petal	X
176	*Rosmarinus officinalis* L.	Rosemary	Lamiaceae	Leaf/ Branch	X
177	*Rubus fruticosus* G.N. Jones	Blackberry	Rosaceae	Fruit	X
178	*Rubus allegheniensis* Porter	Blackberry	Rosaceae	Fruit	√
179	*Rubus idaeus* L.	Red raspberry	Rosaceae	Fruit	X
180	*Rubus ursinus* cv. 'Young'	Youngberry	Rosaceae	Fruit	√
181	*Saccharum officinarum* L	Sugar cane	Poaceae	Stem	X
182	*Salvia officinalis* L.	Sage	Lamiaceae	Leaf	X
183	*Salvia hispanica* L.	Chia	Labiaceae	Seed	X
184	*Sambucus canadensis* L.	Elderberry	Adoxaceae	Fruit	√
185	*Sambucus nigra* L.	Elderberry	Adoxaceae	Fruit	√
186	*Schisandra chinensis* (Turcz.) Baill.	Schisandraberry	Schisandraceae	Fruit	√

Table A1 (continued)

No	Scientific name	Common name	Family	Part used	Imported herbs
187	*Sesamum indicum* L.	Sesame	Pedaliaceae	Seed	X
188	*Solanum torvum* Sw.	Pea eggplant/ Plate brush	Solanaceae	Fruit	X
189	*Spinacia oleracea* L.	Spinach	Amarathaceae	Leaf	X
190	*Syzygium cumini* (L.) Skeels	Black plum/ Jambolan	Myrtaceae	Fruit	X
191	*Tagetes erecta* L.	Marigold	Asteraceae	Bloom	X
192	*Tamarindus indica* L.	Tamarind	Fabaceae	Fruit	X
193	*Taraxacum dens leonis* Desr.	Dandelion	Asteraceae	Root	X
194	*Taraxacum mongolicum* Hard.Maz	Dandelion	Asteraceae	Root	X
195	*Terminalia bellirica* (Gaertn.) Roxb.	Belliric Myrobaran	Combretaceae	Fruit	X
196	*Terminalia chebula* Retz.	Chebulic myrobalan	Combretaceae	Fruit	X
197	*Thymus vulgaris* L.	Thyme	Lamiaceae	Leaf	X
198	*Tremella fuciformis* Berk	White jelly mushroom	Tremellaceae	Mushroom	X
199	*Trigonella-foenum graecum* L.	Fenugreek	Fabaceae	Seed	X
200	*Triticum aestivum* L.	Wheat	Poaceae	Seed	X
201	*Turnera diffusa* Willd. ex Schult.	Damiana	Passifloraceae	Leaf	√
202	*Undaria pinnatifida*	Wakame	Alariaceae	Seaweed	√
202	*Undaria pinnatifida*	Wakame	Alariaceae	Seaweed	√
203	*Vaccinium angustifolium* Aiton	Blueberry	Ericaceae	Fruit	X
204	*Vaccinium myrtillus* L.	Bilberry	Ericaceae	Fruit	√
205	*Vaccinium macrocarpon* Aiton	Cranberry	Ericaceae	Fruit	X
206	*Vaccinium uliginosum* L.	Bog bilberry	Ericaceae	Fruit	√
207	*Vitis labrusca* L.	Bordo grape	Vitaceae	Fruit/ Seed	X

Table A1 (continued)

No	Scientific name	Common name	Family	Part used	Imported herbs
208	*Vitis vinifera* L.	Grape	Vitaceae	Fruit/ Seed/ Bark	X
209	*Vigna radiata* (L.) R. Wilczek	Mungbean	Fabaceae	Seed	X
210	*Zingiber officinale* Rosc.	Ginger	Zingiberaceae	Rhizome	X
211	*Ziziphus jujuba* Mill.	Jujube/ Chinese jujube	Rhamnaceae	Fruit	X

Note √; Imported herbs, X; Cultivated in Thailand, NA; Not available

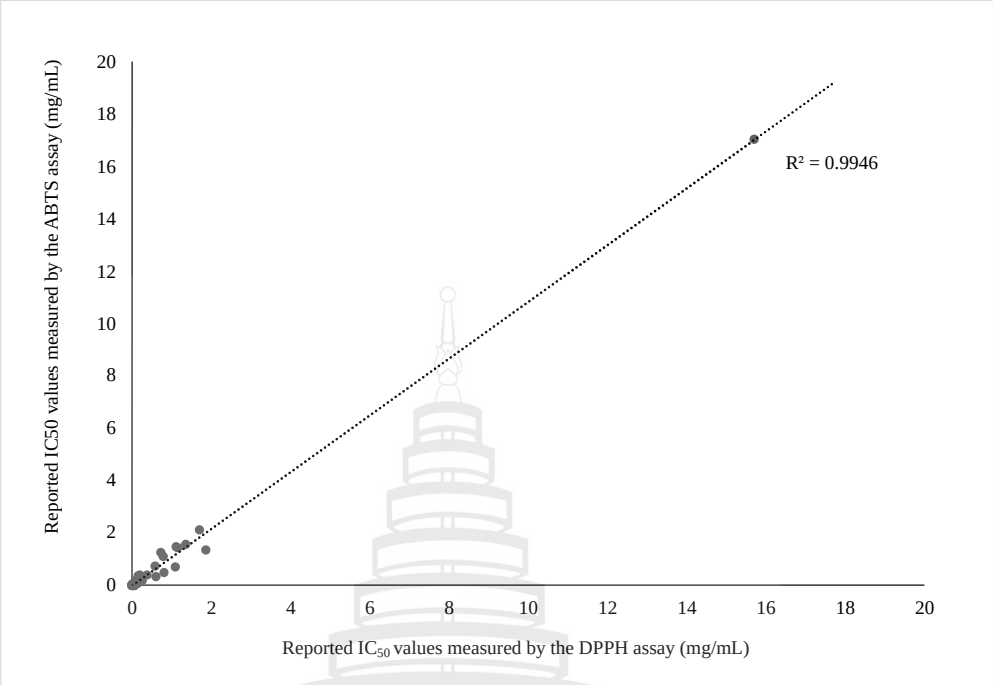

Figure A1 Correlation between the reported IC_{50} values of selected medicinal plants measured by the DPPH and ABTS radical scavenging assays**.** The correlation coefficient, r = 0.993 (*p<0.001*), and the coefficient of determination, R^2 = 0.9946 were calculated.

Table A2 Reported chemical markers of candidate plant-based antioxidants chosen from the list of Thai FDA-approved dietary supplements obtained from medicinal plants

Scientific name	**Part used**	**Bioactive markers/Analysis items (%; w/w)**		
		Compounds	**Required**	**Reported**
Allium sativum	Bulb	Allicin	> 1.00	1.20
Aloe vera	Gel	Aloin content	NA	NA
Bacopa monnieri	Whole plant	Bacosides	≥ 20.00	21.24
Camellia sinensis	Leaf	Polyphenols	> 10.00	10.40
Capsicum annuum	Fruit	Capsaicin	≥ 10.00	12.40
Carthamus tinctorius	Flower	Flavonoids	> 300.00	375.10
Centella asiatica	Leaves	Asiaticoside	> 2.50	2.82
		Triterpene	> 1.00	1.74
Citrus x *aurantium*	Immature fruit	Hesperidin	> 99.00	99.91
Coffea arabica	Seeds	Chlorogenic acid	≥ 50.00	50.25
Curcuma longa	Rhizome	Curcumin	> 5.00	7.40
Daucus carota	Root	Beta-carotene	≥ 10.00	13.67
Ganoderma lucidum	Fruiting body	Polysaccharides	> 50.00	72.80
		Triterpenoids	> 1.00	1.50
Garcinia mangostana	Peel	Xanthone	> 1.00	1.30
Gynostemma pentaphyllum	Leaves	Saponins	≥ 1,000.00	1,392.00
Kaempferia parviflora	Rhizome	Flavonoids	> 1.50	1.51
Matricaria chamomilla	Flower	Apigenin	> 1.00	1.26
Moringa oleifera	Leaf	Flavonoids	> 500.00	567.10
Piper nigrum	Seed	Piperine	≥ 10.00	10.20
Tagetes erecta	Flower	Lutein	≥ 10.00	10.26
Terminalia chebula	Fruit	Gallic acid	≥ 500.00	603.90
Zingiber officinale	Root/ Rhizomes	Total Gingerols	≥ 5.00	5.21

Note NA; Not available

Table A3 Product details of medicinal plants

Scientific name	Trade name	Product number	Origin
Allium sativum	Garlic extract powder	No. TS1NAS71A	Thailand
Aloe vera	*Aloe vera* gel spray dried powder	No. 219021211	Mexico
Bacopa monnieri	Bacopa Extract	No. BCP-2207147	India
Camellia sinensis	Green tea extract powder	No. TS14CAS71A	Thailand
Capsicum annuum	Capsicum tea extract	No. TS18CAF71A	Thailand
Carthamus tinctorius	Safflower extract powder	No. TS12CAT71A	Thailand
Centella asiatica	*Centella asiatica* extract powder	No. TS15CEA71A	Thailand
Citrus x *aurantium*	Citrus bioflavonoids	No. MC-PE-210809C	China
Coffea arabica	Green coffee bean extract	No. BNPGCB210526	China
Curcuma longa	Turmeric extract powder	No. TS13CUL17A	Thailand
Daucus carota	Carrot extract	No. MC-PE-210726A	China
Ganoderma lucidum	Reishi extract powder	No. TS0NGAL71D	Thailand
Garcinia mangostana	Mangosteen extract powder	No. TS11GAM71A	Thailand
Gynostemma pentaphyllum	Jiaogulan extract powder	No. TS13GYE71A	Thailand
Kaempferia parviflora	Black galingale extract powder	No. TS17KAP71A	Thailand
Matricaria chamomilla	Chamomile extract	No. CHP-210713	China
Moringa oleifera	Moringa extract powder	No. TS18MOO73A	Thailand
Piper nigrum	Black pepper extract	No. CHHJ-C-A012795	China
Tagetes erecta	Marigold extract	No. MRE-210724	China
Terminalia chebula	Terminalia extract powder	No. TS19TE71B	Thailand
Zingiber officinale	Ginger extract	No. GOR-2105050	India

Table A4 Ingredients of extruded snack products

Ingredients (%) formula	**Control formula**	**Curcumin microcapsule**
Sung yod rice	78.5	78.5
Green banana flour	20	20
Salt	0.5	0.5
Rice bran oil	1	1
Percentage per all ingredients		
Stabilizer (INS460ii): cellulose	1.0%	1.0%
Sodium carbonate	0.5%	0.5%
sCL11064 powder	-	0.25%

Table A5 Condition used in forming extruded snack products with an extruder

Condition in forming	**Control formula**	**Curcumin microcapsule formula**
Feeding valve (L/hr)	1.0	1.0
Feeder (kg/hr)	20	20
Screw motor (rpm)	400	400
Cutter (rpm)	600	600
Temperature1 (°C)	40	40
Temperature2 (°C)	80	80
Temperature3 (°C)	110	110
Temperature4 (°C)	120	120
Temperature5 (°C)	155	155
Temperature6 (°C)	140	140

APPENDIX B

RESULTS

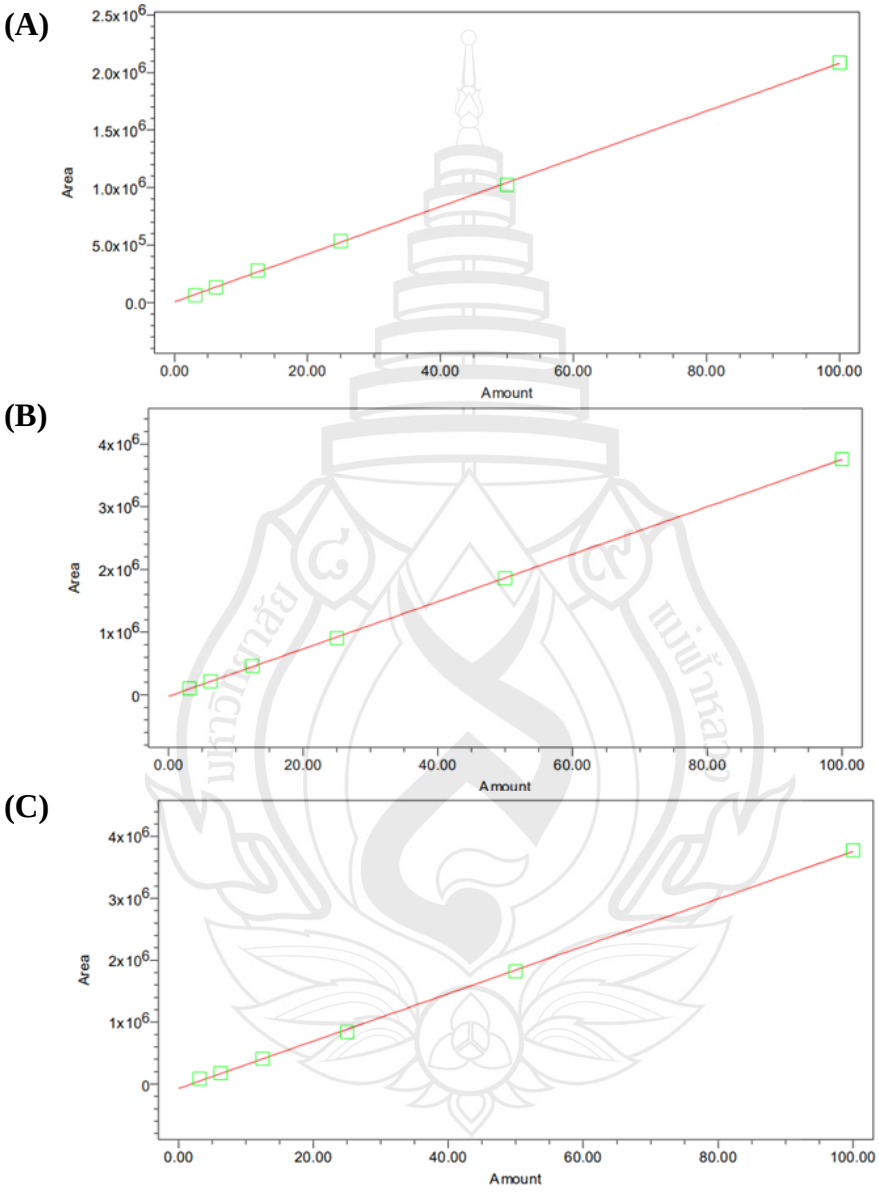

Figure B1 The calibration curve of curcuminoid standard. (A) Curcumin, (B) Demethoxycurcumin (DMC), and (C) Bisdemethoxycurcumin.

Table B1 General characteristics and health behavior of participants

Characteristics	**HFCb**	**RFCb**
Total of number (n=100)	50%	50%
Gender		
Male	31.37%	17.65%
Female	68.63%	82.35%
Status		
Single	54.90%	74.51%
Married	43.41%	21.57%
Unspecified	1.96%	3.92%
Age		
20-29 years	31.37%	39.22%
30-39 years	27.45%	39.22%
40-49 years	23.65%	15.69%
More than 50 years	17.65%	5.88%
Occupation		
Student	-	7.84%
Government official	27.45%	17.65%
Business owner	15.69%	5.88%
Private sector employees	41.18%	56.86%
Freelancer	11.76%	11.76%
Pensioner	3.92%	-
Income		
<15,000 baht	7.84%	11.76%
15,000 – 25,000 baht	37.25%	50.98%
25,001 – 35,000 baht	17.65%	19.61%
35,001 – 45,000 baht	11.76%	9.80%
45,001 – 50,000 baht	9.80%	1.96%
More than 50,000 baht	15.69%	5.88%

Table B1 (continued)

Characteristics	HFCb	RFCb
Residence		
Bangkok metropolitan region	23.53%	31.37%
Provincial in the district	45.10%	45.10%
Provincial	31.37%	23.53%
Health checkup behavior		
Regular health check-ups	27.45%	21.57%
No health check-ups	72.55%	78.43%
Exercise frequency behavior		
0 time/week	23.53%	35.29%
1-2 times/week	35.29%	64.71%
3-4 times/week	35.29%	-
5-6 times/week	23.53%	-
7 times/week	5.88%	-
Alcohol drinking behavior		
No drinking	64.71%	23.53%
Drink on occasion	35.29%	74.51%
Drink always	-	1.96%
Sleep behavior		
Get enough rest	88.24%	74.51%
Not enough rest	11.76%	25.49%
Healthy eating behavior		
Daily	7.84%	-
Always	25.49%	17.65%
Sometimes	62.75%	56.86%
Seldom	3.92%	23.53%
Never	-	1.96%

Table B1 (continued)

Characteristics	**HFCb**	**RFCb**
Interest level in extruded snacks		
Very interest	94.12%	90.20%
Interest	5.88%	9.80%

Note HFCb; Healthy food consumption behavior and RFCb; Regular food consumption behavior

Table B2 Mean liking score for sensory properties of each group of testers towards the appearance of extruded snacks

Sensory attribute	**HFCb**	**RFCb**
Overall liking	7.8 ± 1.1^{a}	6.9 ± 1.5^{b}
Overall odor	7.2 ± 1.4^{a}	6.5 ± 1.5^{b}
Overall flavor	7.4 ± 1.2^{ns}	6.8 ± 1.7^{ns}
Overall testing	7.8 ± 1.2^{a}	6.9 ± 1.7^{b}
Appearance	7.5 ± 1.2^{a}	6.7 ± 1.5^{b}
Texture	8.0 ± 1.0^{a}	7.5 ± 1.4^{b}
After taste	7.8 ± 1.1^{a}	7.1 ± 1.5^{b}

Note HFCb; Healthy food consumption behavior, RFCb; Regular food consumption behavior

^{a,b}; The difference in the mean liking score of each group of testers was statistically significant ($p\leq0.05$), and ^{ns}; No statistically significant difference in the mean liking score of each group of testers ($p>0.05$)

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Awaeloh, N., Kaewmanee, T., & Chusri, S. (2025). Evaluation of *in vitro* antioxidant activities of microcapsules contained standardized turmeric extract (*Curcuma longa* L.) as a core material. *Proceedings of the Phayao Research Conference 14*. (pp. 540-551). Phayao University, Phayao.

Awaeloh, N., Limsuwan, S., Na-Phatthalung, P., Kaewmanee, T., & Chusri, S. (2025). Novel development and sensory evaluation of extruded snacks from unripe banana (Musa ABB cv. Kluai 'Namwa') and rice flour enriched with antioxidant-rich *Curcuma longa* microcapsules. *Foods, 14*(2), 205.