DOCUMENTATION, ANTI-AGING ACTIVITIES AND PHYTOCHEMICAL SCREENING OF SELECTED MEDICINAL PLANTS USED BY JAKUN WOMEN IN KAMPUNG PETA, MERSING, JOHOR

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DEDICATION

For my *abah* (En. Ismail Bin Ebrahim) and *mama* (Pn Siti Habsah Bt. Hashim),
who always inspired me with their hardwork and successs,
who always love, pray and give endless support to their children.

And also for my lovely siblings (Izzati, Nabila & Amir) for their constant motivation and support along this journey.

May Allah reward them with Jannah

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ABSTRACT

Traditional knowledge of indigenous people could become the baseline information for the discovery of anti-aging agent. The objectives of this study were to document the knowledge of Jakun people in Kampung Peta, Mersing, Johor on medicinal plants for women's healthcare; to investigate the optimal formulations of herbal mixture used by Jakun women based on phytochemicals content and antioxidant activity; to determine the anti-aging potential of the selected formulations; and to investigate the major phytochemical constituents in the formulations. Based on qualitative analysis from semi-structured interview, twelve species of medicinal plants have been documented for women's healthcare. Among species documented, four species, *Cnestis palala* (Pengesep), *Urceola micrantha* (Serapat), *Labisia pumila* (Kacip fatimah) and *Microporus xanthopus* (Kulat kelentit kering) that were prepared in the form of mixture have been used for formulation study. About 24 formulations have been developed from the simplex centroid design and tested for total phenolic content (Folin-Ciocalteu method), total flavonoid content (aluminium chloride colorimetric method) and three different antioxidant assays (DPPH scavenging, ABTS decolourization and FRAP assays). Single formulation of *Cnestis palala*, single formulation of *Urceola micrantha* and binary mixture of *C. palala* and *U. micrantha* are among the optimal formulations with high phytochemicals content and antioxidant activities that were further evaluated for anti-aging activities. For anti-aging activities, five enzymatic assays have been tested on the three formulations which are matrix metalloproteinase-1 (MMP-1) inhibition, elastase inhibition, tyrosinase inhibition, acetyl- and butyrylcholinesterase inhibition assays. Single formulation of *U. micrantha* showed the highest inhibition towards MMP-1 (49.44 ± 4.11 %) and elastase enzymes (20.33±2.52%), while single formulation of *C. palala* showed highest inhibitions towards tyrosinase (14.06±0.31%), acetylcholinesterase (32.92±2.13%) and butyrylcholinesterase (34.89±2.84%) enzymes. The identification of phytochemicals compound have been carried out using gas chromatography-mass spectrometer (GC-MS), which showed the presence of 2,2-dimethoxybutane and 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP) in the three formulations extract. The presence of catechol and quinic acid in *U. micrantha* extract might possibly contribute to anti-aging activities of the extract. These findings could become baseline for the exploration of novel anti-aging agents from natural source by using the traditional knowledge of indigenous people.

ABSTRAK

Pengetahuan tradisi orang asli boleh menjadi maklumat asas kepada penemuan agen anti-penuaan. Objektif kajian ini adalah untuk mendokumenkan pengetahuan orang Jakun di Kampung Peta, Mersing, Johor terhadap tumbuhan ubatan yang digunakan untuk penjagaan kesihatan wanita; untuk mengkaji formulasi optimum bagi campuran herba yang digunakan oleh wanita Jakun berdasarkan kandungan fitokimia dan aktiviti antioksida; untuk menentukan potensi anti-penuaan bagi formulasi terpilih; dan untuk mengkaji komposisi fitokimia dalam formulasi. Berdasarkan analisis kualitatif dari temu bual separa berstruktur, dua belas spesies tumbuhan ubatan telah didokumenkan bagi penjagaan kesihatan wanita. Dari spesies yang telah didokumenkan, empat spesies, *Cnestis palala* (Pengesep), *Urceola micrantha* (Serapat), *Labisia pumila* (Kacip Fatimah) dan *Microporus xanthopus* (Kulat kelentit kering) yang di sediakan dalam bentuk campuran digunakan bagi kajian formulasi. Sekitar 24 formulasi telah dibangunkan menggunakan reka bentuk simpleks sentroid dan diuji untuk jumlah kandungan fenolik (kaedah Folin-Ciocalteu), jumlah kandungan flavonoid (kaedah kolorimetrik aluminium klorida) dan tiga asai antioksida (asai penghapusan DPPH, penyahwarnaan ABTS dan FRAP). Formulasi tunggal *Cnestis palala*, formulasi tunggal *Urceola micrantha* dan campuran perduaan *C. palala* dan *U. micrantha* adalah antara formulasi optimal dengan kandungan fitokimia dan aktiviti antioksida yang tinggi, yang dinilai bagi aktiviti anti-penuaan. Bagi aktiviti anti-penuaan, lima asai enzim telah diuji bagi tiga formulasi, iaitu asai perencatan matriks metalloproteinase-1 (MMP-1), perencatan elastase, perencatan tirosinase, perencatan asetil- dan butirilkolinesterase. Formulasi tunggal *U. micrantha* menunjukkan perencatan yang tinggi terhadap MMP-1 (49.44 ± 4.11 %) dan enzim elastase (20.33 ± 2.52% perencatan), mankala formulasi tunggal *C. palala* menunjukkan perencatan yang tinggi terhadap enzim-enzim tirosinase (14.06 ± 0.31%), asetilkolinesterase (32.92 ± 2.13%) dan butirilkolinesterase (34.89 ± 2.84%). Pengenalpastian sebatian fitokimia telah dijalankan menggunakan kromatografi gas-spektrometri jisim menunjukkan kehadiran 2,2-dimetoksibutane and 2,3-dihidro-3,5-dihidroksi-6-metil-4H-pyran-4-one (DDMD) di dalam tiga ekstrak formulasi. Kehadiran katekol dan asid kuinik dalam ekstrak *U. micrantha* berkemungkinan dapat menyumbang aktiviti anti-penuaan bagi ekstrak. Penemuan ini dapat menjadi asas kepada penerokaan agen anti-penuaan yang baharu dari sumber semulajadi dengan menggunakan pengetahuan tradisi orang asli.

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LIST OF SYMBOLS AND ABBREVIATION

˚C	-	Celsius
h	-	Hour
L	-	Liter
mL	-	Milliliter
mg	-	Milligram
min	-	Minute
µL	-	Microliter
µM	-	Micromolar
µU	-	Microunit
nm	-	Nanometer
R^2	-	Coefficient of determination
Aβ	-	Amyloid Beta
ABS	-	Access and benefit sharing
ABTS		2,2’-Azino-bis(3-ethylbenzothiazoline-6-sulphonic acid
AChE	-	Acetylcholinesterase enzyme
AD	-	Alzheimer’s Disease
AP-1	-	Activator protein-1
BuChE	-	Butyrylcholinesterase enzyme
$CaCl_2$	-	Calcium chloride
CBD	-	Convention on Biological Diversity
CE	-	Catechin equivalent
DMSO	-	Dimethylsulfoxide
DNA	-	Deoxyribonucleic acid
DOE	-	Design of Experiment
DDMP	-	2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one
DPPH	-	2,2-diphenyl-1-picrylhydrazyl
DTNB	-	5,5'-dithio-bis-[2-nitrobenzoic acid]
ECM	-	Extracellular matrix

FDA	-	Food and Drug Administration
FRAP	-	Ferric-reducing antioxidant power
GAE	-	Gallic acid equivalent
GC-MS	-	Gas Chromatography- Mass Spectrometry
HEPES	-	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
IK	-	Indigenous knowledge
JAKOA	-	Department of Orang Asli Development
L-DOPA	-	L-dihydroxyphenylalanine
MAPK	-	Mitogen-activated protein kinase
MMP	-	Matrix metalloproteinase
MRNA	-	Messenger ribonucleic acid
NNGH		N-Isobutyl-N-(4-methoxyphenylsulfonyl) glycylhydroxamic
PIC	-	Prior Informed Consent
PTNJ	-	Johor National Park Corporation
ROS	-	Reactive oxygen species
TBARS	-	Thiobarbituric acid reactive substance
TEAC	-	Trolox equivalent antioxidant capacity
TFC	-	Total flavonoid content
TK	-	Traditional Knowledge
TMK	-	Traditional Medicinal Knowledge
TNJER	-	Taman Negara Johor Endau Rompin
TPC	-	Total phenolic content
TPTZ	-	2,4,6-tripyridyl-S-triazine
TRP-1	-	Tyrosinase related protein 1
UV	-	Ultra violet
VMS	-	Volatile methylsiloxane
WHO	-	World Health Organization

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LIST OF PUBLICATIONS

Journals :

i. **Ismail, N. A.,** Abu Bakar, M. F., Kormin, F., Linatoc, A. C., Maryati, M. 2017. Application of statistically mixture simplex-centroid design to optimize the TPC and TFC on the proportion of polyherbal formulation used by Jakun women. *Journal of Engineering & Applied Science* (SCOPUS). [Accepted].

ii. **Ismail, N. A**., Abu Bakar, M. F., Kormin, F., Maryati, M., Akim, A., Isha, A. Anti-aging potential and phytochemical screening of optimal formulations from selected medicinal plants used by Jakun women in Kg. Peta, Johor. *Oxidative Medicine and Cellular Longevity* (SCOPUS). [Submitted]

Proceedings/ Conference/Seminars :

i. **Ismail, N. A**., Maryati, M. & Abu Bakar, M. F. (2015). Medicinal Plants Used For Women's Healthcare Among The Jakun Community In Kg. Peta : A Preliminary Study. In O. Asiah, H. Lim, B. Chee, M. N. Musaadah, M. Mastura, K. Getha, S. Vimala (Eds.), *Proceeding FRIM No. 7* Persidangan Industri Herba (pp. 303–308). Putrajaya: Forest Research Institute Malaysia

CHAPTER 1

INTRODUCTION

1.1 Background of study

Aging is inevitable and considered as natural biological process. However, the changes in physiology of human due to aging are undesirable. Aging is physiologically characterized as a continuous, generalized systemic organ dysfunction, which lead to the increased vulnerability to environmental challenge and increase the tendency to suffer diseases and death. Generally, the incidence of degenerative diseases such as osteoporosis, cardiovascular disease, type 2 diabetes, cancer and Alzheimer's disease escalated with increasing age (Si & Liu, 2014) .

Physically, the obvious sign of aging could be seen on the skin with the formation of wrinkles and atypical pigmentation (Masaki, 2010). The skin condition such as epidermal thinning, reduction in dermal collagen content, decreased in laxity diminished skin moisture, and impaired wound healing have been reported in post-menopausal women (Irrera *et al*., 2017). Exposure of skin to extrinsic factors (environmental aggressor such as UV radiation and smoking) is in the 4th rank that contribute to the nonfatal disease burden and the effects arise as humans get older (Tobin, 2017).

Brain also would be affected as person aged. Normal aging will cause decline in brain function and increase the tendency to suffer from neuronal degeneration. The decline in brain cholinergic system, that contribute to memory function will eventually lead to various age-related neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease (AD), multiple sclerosis, Huntington disease and amyotrophic lateral sclerosis (Solanki *et al*., 2016). Other than individual genetic factors, the external factors such as nutrition, smoking, alcohol, environmental conditions could contribute to the aging in human. Oxidative stress has been identified to be one of the major factors that accelerates the aging process (Rahal *et al*., 2014). Oxidation will cause oxidative injury to the neuron and skin structure. Antioxidant compounds are able to defend human body from oxidation process. Eventhough human body contains its own self defense system, it is insufficient to fight against the cumulative damage due to reactive oxygen species (ROS).

Plants are known to contain numerous bioactive compounds which could potentially act as antioxidant with anti-wrinkle and anti-Alzheimer's properties that protect the skin against key enzyme in wrinkle formation and brain from aging (Nema *et al*., 2011). The exploration of medicinal plants as potential for anti-aging supplement or drugs are rapidly growing for the past few years. According to Global Industry Analyst, nutricosmetic market is estimated to reach US$ 7.4 bilion by 2020, driven by "beauty from within" trend (Analyst, 2015). This indicates that people worldwide are constantly searching for the intervention with nutraceutical benefit that could lead to the improvement and maintenance of their appearances and internal health. The nutricosmetic is the result of convergence between nutraceutical and cosmaceutical field with major claim as an anti-aging (Anunciato & Filho, 2012). The examples of nutricosmetic products include "beauty pills", tablets, liquid (i.e herbal tea), granulates or foods formulation which is believe to be able to reduce wrinkle formation by fighting free radicals generated by solar radiation (Taeymans *et al*., 2014).

More than 89 medicinal plants have been used for cosmetic applications in Malaysia, such as *Centella asiatica* (Apiaceae), *Cosmos caudatus* (Asteraceae), *Curcuma xanthorrhiza* (Zingiberaceae) and *Ficus deltoidea* (Moraceae) are traditionally known to preserve youthful appearance of women (Narayanaswamy & Ismail, 2015). Usually, these plants contain antioxidant with anti-wrinkle properties. In spite of the wrinkle inhibition, the antioxidant also possess cholinesterase inhibitory activities which is one of the treatment in AD prevention. In a review by Natarajan *et al*. (2013) on Asian plants, more than 40 herbal remedies have been used traditionally and being proven scientifically to possess anti-inflammatory, anti-cholinesterase andantioxidant activities, which are contributed by its bioactive compounds such as alkaloids, flavonoids, steroids, saponins, terpenoids and essential oils. Despite the progress made in aging and Alzheimer's disease research in the last decades, no treatment with a strong disease-modifying effect is currently available (Natarajan *et al*., 2013).

Traditional knowledge (TK) on medicinal plants has been one of the sources in drug discovery from natural sources. TK has been defined as the knowledge, innovations and practices of indigenous and local communities around the world which were developed from experience gained over the centuries and adapted to local culture and environment, and transmitted orally from generation to generation (MoNRE, 2012). Traditional Medicinal Knowledge (TMK) is one of the sub categories of TK, other than traditional agricultural and ecological knowledge (Van Overwalle, 2005). According to World Health Organization (WHO, 2003), about 80% of people around the world utilize traditional medicine as their primary healthcare whereas 65% of citizen in developing nation use traditional medicine as an alternative to their healthcare maintenance. In National Policy on Biological Diversity 2016-2025, TK has been highlighted to be one of the key elements in conservation and sustainable uses of biodiversity (MoNRE, 2012). In addition, Malaysia has implemented an act on Access to Biological Resources and Benefit sharing bill 2017 in order to preserve the traditional knowledge of local and indigenous people, and also to ensure the fair and equitable sharing from the knowledge provided by the indigenous people.

Malaysia is ranked 12th among countries of the world with megabiodiversity and at least 95 subgroups of indigenous people that make up Malaysia's multiracial population (Masron *et al*., 2013). The wonderful knowledge and respect towards plants have originated from indigenous people, usually called 'Orang Asli', who inherited the knowledge and practices from their ancestors (Adnan & Othman, 2012). The indigenous and local communities usually live in an area where majority of plants genetic resources are found. In this regard, the preservation of the TK through documentation is crucial to maintain the biodiversity in Malaysia (MonRE, 2012). However, TK suffer from erosion and biopiracy. These documentation is the utmost defensive approach for conserving the TK from erosion, acquisition and exploitation by third parties (Van Overwalle, 2005).

Jakun, Orang Kuala, Orang Kanaq, Orang Seletar and Temuan are ethnic groups recognized as orang asli that live in the southern part of Malaysia, Johor (Masron *et al*., 2013). The Jakun tribe, who live in Kampung Peta, Endau, Mersing, Johor are the holder and users of TK. Despite modernization of this country, most of the older generations in Jakun community still rely on traditional medicine for their healthcare. They utilize plants and animals to treat various ailments. The earliest record of ethnomedicinal knowledge of Jakun on plants has been documented by Taylor & Wong (1987), whereas the recent documentation of plant by Jin (2005) include the use of palm for medicinal purposes, Ismail *et al*. (2015) on the medicinal plants used for malarial treatment and Sabran *et al.* (2016) on medicinal plants used for treatment of tuberculosis. However, no study has been focusing on the use of medicinal plants specifically for maintenance of women's healthcare in Jakun community. The Convention on Biological Diversity (CBD) has recognized the role of women and local communities in conservation of biological diversity. In fact, a review on medicinal plants used for women healthcare in South-East Asia revealed 2000 different plant species have been used in 5000 combinations to treat various ailments for women (Boer & Cotingting, 2014). There is a clear need to document the TK of women in Jakun community on the use of medicinal plants, particularly in health and beauty maintenance.

While taking into account the individual medicinal plants for the treatment of disease, the consumption of traditional herbs in the form of mixture is believed to exert higher pharmacological and therapeutic efficacy compared to the single medicinal plants (Guimarães *et al.*, 2011; Wang *et al*., 2014). Few reported studies showed that mixture of medicinal plants exhibit higher bioactivities compared to the single plants (Xu *et al*., 2014). The mixture is said to be able to increase the medicinal properties of individual species, reduce toxicity and improve the taste acceptance (Guimaraes *et al*., 2013). In traditional chinese medicine (TCM), some of the anti-dementia herbal formulation have been proved scientifically to exert dementia inhibition effect (Kong *et al.*, 2009). The different herbs exert different effects and when combined, it acts either in synergistic, antagonistic or additive manner. The knowledge regarding the herbal mixture have been passed from older generation to the current generation of herbal practitioner and skillfull healer. Traditionally, the herbal plants that was prepared as mixture have similar therapeutic effects and benefits with possible of synergistic effects (Boer & Cotingting, 2014; Guimaraes *et al*., 2013). Based on the documentation by Taylor & Wong (1987) in Jakun community, some ailments could be treated by mixture of medicinal plants. Thus, the documentation of medicinal plants for women's healthcare maintenance and investigation on the herbal mixture used by Jakun women for anti-aging might provide the baseline data for the exploration of anti-aging treatment.

1.2 Problem statement

Aging has been associated with undesirable effects towards physiology and psychology of a person. Although many treatments have been applied to cure or delay these pathologies, it have been found to be ineffective or associated with side effects. Nutricosmetic product with anti-aging claim has increased its popularity in the market, eventhough the efficacy of this product has not been proven scientifically (Draelos, 2010).

Furthermore, the prevalence of neurodegenerative diseases also increase yearly. According to Alzheimer's Disease Foundation Malaysia (ADFM), currently, it is estimated that 50,000 Malaysians suffer from Alzheimer's disease. The incidence of AD could double every five years beyond the age of 65. Although some of the drugs been approved by United State Food and Drug Administration (FDA) for the treatment of AD (i.e Donepezil, Galantamine, Rivastigmine, and Huperzine A), the outcomes are often unsatisfactory (Natarajan *et al*., 2013; Association, 2014) and associated with side effects such as headache, diarrhoea, drowsiness and vomiting among others.

With regards to the mentioned problems, there is a great demand to develop a safe and more effective cure for skin and brain aging, and medicine to cure and treat these undesirable conditions. Traditional knowledge which is one of the resources in drug discovery is vulnerable to multiple factors, such as erosion and modernization (WIPO, 2001). Thus, the documentation of TK and the investigation on the bioactivities of selected plants might preserve the knowledge and validate the traditional claim.

1.3 Objectives

This study aimed to integrate the traditional knowledge of indigenous people for women health maintenance and to investigate scientifically the potential of the medicinal plants for anti-aging. This aim could be achieved through following specific objectives:

i. To document the knowledge of Jakun people on medicinal plants for women healthcare.
ii. To determine the optimal formulations of selected herbal mixture used by Jakun women based on phytochemicals content and antioxidant activities.
iii. To determine the anti-wrinkle (elastase and collagenase inhibition activities) and anti-hyperpigmentation (tyrosinase inhibition activity) of optimal formulations.
iv. To determine the anti-Alzheimer potential (acetylcholinesterase inhibition and butyrylcholinesterase inhibition activities) of optimal formulations.
v. To profile the phytochemical constituents of the selected plants extracts that potentially contributed to the anti-aging properties of optimal formulations.

1.4 Significance of study

In recent years, increasing attention has been paid in searching for solution to reduce the effect of aging. While most of the products with anti-aging claim contain synthetic chemicals which harmful to human, medicinal plants with diverse phytochemicals has been shown to be a better solution as anti-aging agent (Kapoor, Dureja, & Chadha, 2009a). Findings from this study provide scientific evidence on the potential of medicinal plants as anti-aging agent by employing the traditional knowledge of Jakun people on medicinal plants. Besides that, this finding also provides the evidence on the synergistic effects of herbal mixture that is usually believed to be able to exert more therapeutic effects (Guimaraes *et al*., 2011) as compared to the single herbs. Thus, the evidence of this study will be useful in selecting the formulations with more health benefits and anti-aging effects.

CHAPTER 2

LITERATURE REVIEW

2.1 Documentation of traditional knowledge

2.1.1 Definition of terms

The Convention on Biological Diversity (CBD) in Article 8 (j) has described the term traditional knowledge as :

> …. the knowledge, innovations and practices of indigenous and local communities around the world, developed from experience gained over the centuries and adapted to the local culture and environment, and transmitted orally from generation to generation. It tends to be collectively owned and takes several forms from stories, songs, folklore, proverbs, cultural values, beliefs, rituals, community laws, local language and agricultural practices, including the development of plant species and animal breeds. (MoNRE, 2012)

The term "traditional" does not refer to "old", but it is rather the traditions that have been passed from generations to generations. It relates to the way the knowledge has been created, preserved and disseminated (Finetti, 2011). Traditional Knowledge (TK) comprise of tangible and non-tangible elements (WIPO, 2012). The tangible element of TK is the genetic resources, while the intangible element is the knowledge. The TK sometimes refers as indigenous knowledge (IK). The IK is actually a subset of TK, where the users are communities, people and nation that are indigenous (Van Overwalle, 2005) and the knowledge is only known by the specific community (Finetti, 2011). The traditional knowledge could be further classified into three categories, which are traditional medicinal, agricultural and ecological knowledge (Van Overwalle, 2005). Traditional medicine is defined as the compilation of knowledge, skills and practices based on theories, belief and experiences native to different cultures, where understandable or not, used for health maintenance as well as in the prevention, diagnosis, improvement or treatment of mental and physical illness (WHO, 2000)

Documentation of TK is defined as a process of identifying, collecting, organizing, registering or recording TK, in order to maintain, manage, use, disseminate and/or protect TK according to specific aims. This knowledge is not limited to simple photographing, or isolated record of tradition, or written notes, but the isolated act need to undergo comprehensive, thought-through process to be regarded as ‘documentation’. The most significant thing that needs to be considered while documenting TK is consultation (with and among indigenous or local people), participation and prior informed consent (PIC) before the documenting process starts (WIPO, 2012).

The traditional medicine usually involves all organisms such as animals, plants, and microbes in the treatment of illness by local or indigenous people. Another term that is usually being used in traditional knowledge field is ethnobotany. Ethnobotany and ethnopharmacology are interdisciplinary field that focused on empirical knowledge of indigenous people regarding medicinal substances, their potential health benefits and side effect associated with such remedies (Gurib-fakim, 2006). Ethnobotany has not only restricted to plants, but also involves the studies of algae, lichens and fungi (Eldeen *et al*., 2016). In the current study, the utilization of medicinal plants, including fungi were investigated among Jakun women in Kampung Peta.

2.1.2 The importance of documenting the traditional knowledge

2.1.2.1 Conserving genetic resources and natural heritage

The traditional knowledge on the uses of organisms including animals in traditional medical system, is important to be documented as the biodiversity is eroding from day to day (Alves & Rosa, 2007). Destructive exploitation of the tropical forest such as illegal logging and conversion of forest to plantation have become the key to the loss of biodiversity and global climate. The precious medicinal plants which have the potential to be developed as useful drugs might be lost along with the forest degradation. In Malaysia, the TK documentation is increasing. Likewise, Forest Research Institute Malaysia (FRIM) with other organizations and universities are moving forward with the effort of documenting the TK of Orang Asli in Peninsular Malaysia (Fui *et al*., 2015).

2.1.2.2 Intellectual property and protection against biopiracy

Before the implementation of CBD, little attention has been given to the issues of sustainable development and sharing of benefit with knowledge holder (Fui *et al*., 2015). This has led to biopiracy towards TK. Biopiracy refers to the illegal extraction and exploitation of TK and/or related biological and genetic resources and/or the acquisition of intellectual property right (IPR) over the resultant inventions that originate from knowledge or resources without provision for benefit-sharing with the individuals or community that provide the knowledge or resources (WIPO, 2001). In other words, biopiracy is invasion to the unprotected indigenous resources, including traditional knowledge (Eldeen *et al.*, 2016).

In traditional medicine, several cases of biopiracy have attracted international attention, as such, the case of turmeric (*Curcuma longa*) in the treatment of wound, the use of neem (*Azadirachta indica*) extract as fungicide and the issue of ‘Basmati rice’ (Payumo *et al*., 2009; Finetti, 2011). In 1997, the patent that has been granted by United State patent and trademark office (USPTO) to two researchers from University of Mississippi Medical Centre had been cancelled. This is due to the request of re-examination by the Council of Scientific and Industrial Research (CSIR), India. The evidence for the traditional usage of turmeric for cooking and for the treatment of wound and rashes, have been written in classic Sanskrit manuscript and also has been published in Journal of the Indian Medical Association in 1953 (Finetti, 2011). Such cases arise due to the lack of good documentation on the traditional knowledge. Thus, there is urgent need to have proper documentation in order to prevent biopiracy.

2.1.2.3 Foundation to the drug discovery

Documentation of TK on medicinal plants is a useful approach for discovering the novel chemical compounds and potentially useful drugs (Ong *et al.*, 2011; Weldegerima, 2009) from plant materials, other than randoms, taxonomic and chemotaxonomic approach (Ahmad, 2000). Tropical rainforest contains vast chemical entity that has yet to be fully explored. Some important findings has been highlighted formerly in the ethnopharmacological research. Examples include publications on genetic resources originated from tropical rainforest such as the discovery of Calanolide A from *Calophyllum lanigrum* with anti-HIV activity, taxol from *Taxus brevifolia* for the treatment of ovarian cancer, michellamines A and B alkaloid from *Ancistrocladus abbreviatus* and *Castanospermum austral* with anti-HIV activities (Ahmad, 2000).

Another classical finding in the ethnopharmacology area is the discovery of vincristine and vinblastine from rosy periwinkle (*Catharanthus roseus*; family: Apocynaceae) for the treatment of children leukaemia and Hodgkin disease. About 75 alkaloids has been found in this plant species. *C. roseus* is native to southern Madagascar and locally used as oral hypoglycaemic agent. Likewise, numerous drug available today, such as aspirin, ephedrine tubocurarine, digoxin, reserpine and atrophine and rooted from the traditional knowledge of people around the world (Gurib-fakim, 2006).

2.1.3 Issues in traditional knowledge and ethnobotany

Few issues have become the major concern among TK holders, which are : 1) the erosion of traditional lifestyles and knowledge, and the unwillingness of younger generation to continue the traditional customs; 2) the lack of respect for TK and its holders; 3) the abuse of TK such as the use of TK without benefit sharing or in an offensive approach; 4) the lack of understanding on the needs to preserve and advance the use of TK (WIPO, 2001). Traditional knowledge and ethnomedicinal knowledge is eroded among the indigenous people due to multiple factors. Availability of modern medicine, younger generations are less interested in traditional medicine, habitat and environmental alteration which caused many medicinal plants to be less or not available, are among the factors that lead to erosion of traditional knowledge (Ong *et al.*, 2012). Furthermore, most children or younger generation are sent by their parents to urban area to get proper education and find job in the city. Thus, less time spent for older generation to pass on the knowledge to younger generations.

2.2 Jakun community

Around the globe, majority of indigenous people sited at remote area and rely on the natural resources in the ecosystem for subsistence (Khor & Shariff, 2008). Approximately, there are about 150,000 people in the community of indigenous people or usually called as Orang Asli in Peninsular Malaysia (Lee *et al.*, 2009). The indigenous people could be divided into three major tribes, namely Negrito, Senoi and Proto-Malays. In Johor, the indigenous people from the Proto Malays encompasses of ethnic Kanaq, Kuala, Seletar, Jakun, Semelai, and Temuan (JAKOA, 2017).

Johor is located at the southern part of Peninsular Malaysia, which consist of high distribution of Orang Asli. Majority of Jakun people are usually being called ‘Orang Ulu’ live in Johor. Based on Jabatan Kemajuan Orang Asli (JAKOA) survey in 1995, there are about 16,637 of Jakun ethnic all around Johor. Jakun people or Orang Ulu, is categorised under Proto-Malay group. Most of them settled in the Endau Valley in Northern Johor, known as Kampung Peta, Mersing (Taylor & Wong, 1987).

The Jakun still rely on the forest for livelihood in many ways in which they acquire knowledge about the medicinal plants from their surroundings. Despite of modernization, members in Jakun community still depends on their ancestor’s traditional lifestyle which indicate that the knowledge is still circulating within the community.The Jakun speak Jakun dialect, which is a subdialect of Malay language (Sabran *et al*., 2016). The traditional knowledge systems of indigenous people are special as it includes knowledge of species, ecological interactions and other environmental phenomena, obtained through observation, practice, adaptation and innovation (MoNRE, 2012).

2.3 Ethnomedicinal knowledge of plants

2.3.1 Ethnomedicinal knowledge of plants by the Jakun community

The first documentation of medicinal plants in Kampung Peta has been done by Taylor & Wong (1987) who recorded 52 plant species in 32 families for general medicinal purposes. Jin (2005) has recorded 10 palm species used for medicinal purposes. Additionally, 127 medicinal plants have been recorded for Jakun community (Khazanah Endau Rompin Herba., 2007, Khazanah Endau Rompin Herba., 2008). Recently, the documentation on ethnomedicinal knowledge of medicinal plants for the treatment of malaria and tuberculosis symptom have been documented by Ismail *et al.* (2015) and Sabran *et al*. (2016). Despite the previous documentation being done for Jakun ethnic, none of it has focused on the medicinal plants for maintenance of women's healthcare and beauty.

2.3.2 Medicinal plants for women's healthcare

Rural women and men embodied a wealth of knowledge on ethnomedicinal usage of plants. However, women play more role in collecting, processing, storing and utilising the medicinal plants. In addition, the transmission of traditional knowledge to the next generation was done by women (Singhal, 2005). Women's ethnobotanical knowledge and medicinal roles are often underestimated by ethnobotanists, who tend to make a beeline for the shaman or medicine man. However, these perception has changed, in which the 'common' knowledge of lay women has also regarded as dominant in the traditional health care systems (Good, 1987; McClain, 1989). Kardooni *et al.* (2014) noted that 18.5% of men have knowledge on traditional medicine, whereas, only 14.6% of women in Orang Asli communities embodied the traditional medicinal knowledge, in which the differences are not significant.

Review on medicinal plants used by women's healthcare has been done by Boer & Cotingting (2014). There are about 1875 species which belongs to 211 families and 980 genera of plants have been used by women in Southeast Asia. The same authors have defined the women's health use as any plants reported to increase fertility, ease pregnancy and parturition, reduce menstrual bleeding, abortion, and fetal or placental expulsion, vaginal discharge and post-partum haemorrhage, induce menstruation, alleviate menstrual, parturition and postpartum pain, increase or inhibit lactation and treat mastitis, uterine prolapse and sexually transmitted diseases.

Based on Table 2.1, only few medicinal plants have been recorded for women's health maintenance for indigenous people in Malaysia such as post-partum treatment, health tonic and anti-aging. Thus, current documentation could contribute to the ethnobotanical data of women in Jakun ethnic.

Table 2.1: Ethnomedicinal plants used by indigenous people in Peninsular Malaysia

Tribe	Type	Overall documented medicinal plants	No. of species used for women's health	References
Semang	General	62	2	(Samuel *et al*., 2010)
Kensiu	General	39	7	(Mohammad, Milow, & Ong, 2012b)
Semai	General	37	8	(Ong, Lina & Milow, 2012)
Temuan	General	36	5	(Azliza *et al*., 2012)
Jah Hut	General	53	16	(Ong *et al*., 2012)
Jah Hut	General	16	1	(Lin, 2005)
Temiar	General	26	3	(Rao *et al*., 2016)

2.4 Aging

2.4.1 Terminologies

Aging is a complex phenomenon, resulting from accumulation of changes due to the genetic variation, environmental aggressor, nutrition intake and individual lifestyle that happen in living organism throughout their life time and which reduce their ability to survive stress (Harman, 1998; Ho *et al.*, 2010; Royer *et al.*, 2013). Aging is defined as a process of progressive reduction of "vital energy" in human body, resulting in organ dysfunctions and diseases. Aging can be categorised into normal and pathological aging. Normal aging is a natural maturation process which is characterised by reduction in memory functions, reduced ability to deal with stress, increasing homeostatic imbalance, increased risk of disease and wrinkling of skin due to loss of fat, increase degradation by matrix metalloproteinase (MMP) and reduced synthesis of extracellular matrix principally collagen and elastin (Ho *et al*., 2010). Pathological aging is always associated with non-normative factors such as diseases and brain trauma (Ho *et al.*, 2010). Although aging occurs naturally, it can be postponed or prevented by certain approaches (Kapoor *et al.*, 2009).

2.4.2 Theories of aging

Aging happens at various biological level such as evolutionary, molecular, cellular and system levels in which the explanation of the theories may overlap between each other (Weinert & Timiras, 2003). In cellular level, there are four theories of aging, which are telomere theory (cellular senescence), free radical theory of aging, wear and tear theory and apoptosis theory of aging (Weinert & Timiras, 2003). The cellular senescence theory was proposed by Hayflick (1965). According to Hayflick (1965), normal human cell have limited number of cell division or replication. When the cell reach maximum number of replication, the cell will be arrested with altered physiology. For every cell division, a small amount of DNA will be lost at each chromosome end, resulting in shorter and altered telomeres (specialized structure composed of repeating DNA sequence). In addition, the other types of cell senescence happens due to the induction of stress, known as stress-induced senescence (SIS). Among factors that trigger SIS are DNA damage, modification of heterochromation structure and strong mitogenic signals resulting from oncogene expression (Weinert & Timiras, 2003).

The most popular theory of aging is free radical theory proposed by Harman (1956). Free radical theory of aging (FRTA) stated that the free radicals, (which are usually generated during metabolic process and also in our environment), caused the deleterious side effect on cell constituents. Currently, FRTA has been widely known as oxidative damage/stress theory of aging, due to the contribution of oxygen species such as peroxides and aldehyde (which technically are not free radicals) in the process of oxidative damage to the cells (Pérez-Hernández *et al.*, 2016). The formation of free radicals and other reactive oxygen species (ROS) during the metabolism process and being triggered by the action of various exogenous factors, could damage biomolecules and lead to the age-related diseases and aging (Sadowska-Bartosz & Bartosz, 2014). For instance, the mitochondrial respiration generate ROS by leaking intermediates from electron transport chain during the energy production in all eukaryotes (Weinert & Timiras, 2003). Thus, by decreasing the rate of initiation and/or chain length of free radical reaction, the aging rate would decrease without affecting the maintenance and function (Harman, 1998).

2.4.3 Role of oxidation in aging

Free radicals are atoms, molecules or ions containing unpaired electrons with unstable and active properties towards chemical reaction with other molecules. Three elements, oxygen, nitrogen and sulfur make up the free radicals which become reactive oxygen species (ROS), reactive nitrogen species (RNS) and reactive sulphur species (RSS) (Carocho & Ferreira, 2013). These free radicals categorized in prooxidant group (Irshad & Chaudhuri, 2002). In human body, the normal metabolic or physiological process will produce ROS and RNS in mitochondria via xanthine oxidase, peroxisomes, inflammation processes, phagocytosis, arachidonate pathways, ischemia, and physical exercise, which play a crucial role in immune response and cell signaling (Carocho & Ferreira, 2013; Omar *et al*., 2017). Among external factors that help trigger the production of free radicals are pollution, UV-radiation, drugs, industrial waste and pesticide (Carocho & Ferreira, 2013). Our endogenous defense system help in maintaining the level of ROS and RNS within the physiologically beneficial limits (Omar *et al*., 2017). The ROS include superoxide, hydroxyl radical and some non-free radical such as singlet oxygen, hydrogen peroxide (Dzialo *et al*., 2016). The imbalance between the production of free radicals with antioxidant will result in pathogenesis of aging and other diseases such as reperfusion injury, atherosclerosis, neurodegenerative disease, cancer, and failures in immunity as well as endocrine function (Matés *et al.*, 1999). The excess accumulation of free radicals inreased the vulnerability of individuals to oxidative insults. These radicals could potenitally caused apoptosis, necrosis and cell death in human body (Irshad & Chaudhuri, 2002).

2.4.4 Aging through skin

2.4.4.1 Mechanism of wrinkle formation

Skin aging happens due to several factors such as reactive oxygen species (ROS) action, mitochondrial DNA mutations, telomere shortening, and hormonal changes (Tobin, 2017). The process of skin aging could be divided into two categories, which are extrinsic aging and intrinsic aging (Thring, 2012). Intrinsic aging or usually called chronological aging is influenced by genetics and hormonal changes, whereas the extrinsic aging caused by the environmental factors such as ultraviolet radiation (UVR), smoking, diet and chemicals (Royer *et al*., 2013). The extrinsic aging is also called photoaging due to the powerful effect of UVR to the skin which result in damaging effect such as wrinkle formation (Rabe *et al.*, 2006; Thring *et al*., 2009; Tobin, 2016). Both types of aging displayed distinct and overlapping features (Tobin, 2017). Approximately, 50% of UV-induced damage is from the formation of free radicals, whereas direct cell injury and other mechanisms account for the remainder of UV effects (Rabe *et al*., 2006).

Human skin is divided into three layers, which are epidermis, dermis and subcutaneous tissue (Ndlovu *et al.*, 2013). Connective tissue in the dermis of human skin is made up of collagen and elastic fibres, which accounts for 70 to 80% of the skin weight, functions to provide structural stability (Hong *et al.*, 2014). Dermal collagen bundle is well organized in young adult. Collagen is important for skin wound healing and skin rejuvenation process (Limtrakul *et al.*, 2016). Another components of extracellular matrix (ECM) are elastin, elastic fibre and hyaluronic acid which are essential for strengthening the facial muscle and moisturize the skin to make it less prone to oxidative stress (Pimple & Badole, 2013; Taofiq *et al.*, 2016). Aging has caused the collagen to increase in density, but loose the extensible configuration which result in fragmented, disorganized and less soluble collagen. (Tobin, 2017). This is due to the alteration at the connective tissues through the formation of lipid peroxide, cell contents and enzyme (Thring *et al.*, 2009).

Epidemiological studies has showed that three enzymes are responsible to the wrinkle formations, which are collagenase, elastase and hyaluronidase (Mukherjee *et al.*, 2011). High level of ROS will trigger the activation of the collagenase, elastase and hyaluronidase (Mukherjee *et al*., 2011; Ndlovu *et al*., 2013). The matrix metalloproteinase, which is collagen degrading enzymes are upregulated during photoaging and intrinsic aging through the production of ROS. In addition, ROS not only destroy the interstitial collagen, but also inactivate tissue inhibitors of matrix metalloproteinases (Tobin, 2017). The inhibition of these enzyme is believed improve the structure of collagen in the ECM and improve the metabolism coordination (Mukherjee *et al*., 2011).

2.4.4.2 Mechanism of hyperpigmentation

Melanin is a mixture of heterogenous biopolymer which synthesizes within melanocyte in specialised organelles called melanosome. It is transferred to keratinocytes and give protection against oxidative stress. Melanin determines the colour of human skin, hair and eyes (Kamagaju *et al*., 2013). The melanin is good for skin. However, it will be unfavourable when it is overproduced which eventually leads to hyperpigmentation such as melasma and ephelids as well as skin deterioration (Atta-ur-Rahman *et al.*, 2005; Royer *et al.*, 2013).

ROS contributes to the skin hyperpigmentation. Among ROS, nitric oxide radicals derived from keratinocyte induce melanogenesis by increasing the amount of melanogenic factor tyrosinase and tyrosinase-related protein 1 (TRP-1) (Masaki, 2010). The tyrosinase is a very important enzyme responsible for melanin biosynthesis (Masamoto *et al.*, 1980), which participate in two stages of melanin biosynthesis (Pedrosa *et al*., 2016). The first stage is the hydroxylation of L-tyrosine to 3,4-dihydroxyphenylalanine (L-DOPA) and the second stage, the oxidation of L-DOPA to 4-(2-carboxy-2-arninoethy1)- 1,2-benzoquinone (o-dopaquinone). This o-quinone is highly reactive and produce melanin pigment (Sung *et al*., 2009). In addition, hydrogen peroxide could trigger the production of L-tyrosine (initial substrate of tyrosinase) through the activation of epidermal phenylalanine hydroxylase (enzyme that produce L-tyrosine from the essential amino acid L-phenylalanine), thus, promoting melanogenesis (Masaki, 2010).

2.4.5 Alzheimer's disease and its mechanism

Alzheimer disease (AD) is a genetically complex disorder that accounts for most cases of dementia that happens to older people, usually after 65 years (Villaflores *et al.*, 2012). It was estimated that, by the age of 85, one out of two people develops AD (Patocka *et al.*, 2004). This neurodegenerative disease affects major brain areas including cortex and limb system. Initial symptoms of AD is a loss in short term memory, while the progression of AD is marked by a continuous decline in cognitive function such as abstract thought, language and decision making processes, and disability to carry out daily activities which will affect the surrounding people. The effect is worsen when it further results in depression, psychosis and aggression

(Villaflores *et al.*, 2012; Natarajan *et al.*, 2013; Shakir *et al.*, 2013). In average, the patient suffering AD will die after nine years of diagnosis making the increasing risk of AD is at an alarming state (Natarajan *et al*., 2013).

Generally, the development of AD is believed to be contributed by cholinergic and cerebral blood flow deficits, excessive level of oxidative stress, neuroinflammation and glutamate excitatory mechanisms (Shakir *et al.*, 2013). Eventhough several hypotheses have been proposed for the mechanism of AD pathology, the exact pathophysiological mechanism is still not fully understood. There are four hypothesis involved in pathology of AD, which are i) amyloid cascade hypothesis, ii) tau hypothesis, iii) oxidative stress hypothesis and iv) mitochondrial hypothesis (Omar *et al*., 2017). The amyloid cascade hypothesis postulates that the excessive deposition of extraneuronal senile beta-amyloid (Aβ) plaque and intraneuronal tau protein neurofibrillary tangles (NFT) in the brain triggers neurotoxic cascade which result in neurodegeneration and AD (Villaflores *et al*., 2012; Omar *et al.*, 2017).

The loss of cholinergic function in central nervous system led to the AD. Cholinesterase (ChE) is a family of enzymes that are able to hydrolyze choline esters at faster rate compared to other esters under optimal conditions (Patocka *et al*., 2004). Smith & Cuello (1984) emphasized that the different cells outside the cortex in which the lesion present, contain acetylcholinesterase. Two isoforms of cholinesterase in vertebrates are acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) (Omar *et al*., 2017). AChE, which is also known as true, specific, genuine and type 1 cholinesterase could be found in erythrocyte, nerve endings, lungs, spleen and all components of brain. Whereas, BuChE is usually synthesized in many tissues including liver, lungs, heart and brain (Patocka *et al*., 2004). Most of the cholinesterase activity in healthy human brain is AChE due to its higher concentration compared to BuChE. However, in the late stage of AD, the BuChE is two times higher than AChE in the brain (Omar *et a*l., 2017)

2.5 Intervention of aging

2.5.1 Antioxidant and its mechanism

Antioxidant is defined as a group of endogenous or exogenous molecules which able to delay or inhibit oxidation of a particular substrate, even when presented in low concentration compared to that substrate (Sies, 1985). The antioxidant could be subcategorised into enzymatic and non-enzymatic antioxidant. The enzymatic antioxidants such as superoxide dismutase, catalase, glutathione peroxidase and catalase, whereas the non-enzymatic antioxidant include ascorbic acid, tocopherol, glutathione, carotene and vitamin A. The superoxide dismutase plays a role by catalysing the dismutation of the highly reactive superoxide anion to O_2 and less reactive species of peroxide, H_2O_2. Then, the peroxide can be destroyed by catalase or glutathione peroxidase (Matés *et al.*, 1999). If the reactive species is able to escape the enzymatic degradation by the antioxidant enzyme, it can be terminated with the help of chain-breaking antioxidants including water-soluble ascorbate, lipid-soluble vitamin E, and ubiquinone (Matés *et al.*, 1999).

There are four levels of antioxidant actions, such as preventive, radical scavenging, repair and de novo and lastly, adaptation. The first line defense is the preventive antioxidants, which suppress the formation of free radicals. The examples of antioxidant in this level are glutathione peroxidase, glutathione-s-transferase, phospholipid hydroperoxide glutathione peroxidase (PHGPX) and peroxidase. Antioxidants that scavenge the active radicals to suppress chain initiation and/or break the chain propagation reactions categorized as the second line defense. Hydrophilic antioxidant, such as vitamin C, uric acid, bilirubin, albumin and thiol and lipophilic antioxidant, such as vitamin E and ubiquinol are the examples of second line defense antioxidant level. The third line defense is the repair and de novo antioxidant, in which the proteolytic enzymes, proteinases, proteases and peptidases, present in cytosol and in mitochondria cells, identify, degrade and terminate oxidatively modified proteins and prevent the accumulation of oxidized protein. The DNA repair system plays vital role in the total defense system against oxidative damage. Adaptation level, where the signal for the production and reactions of free radicals induces formation and transport the appropriate antioxidant to the right site (Lobo *et al.*, 2010). Thus, supplying our body with antioxidant nutrients will eventually help in removing the oxidants

There are various mechanisms that could be utilized to analyze the antioxidant potential of plants (Capitani *et al.*, 2009). The antioxidant mechanisms for each assays are different. Therefore, each plant preparation can have different compounds with specific capacities to participate in those mechanisms (Guimaraes *et al.*, 2013). There are two types of approaches to measure the effectiveness of antioxidant potential of the compounds or samples: hydrogen atom transfer (HAT) and single electron transfer (SET). HAT involves the quenching or scavenging of free radicals via hydrogen donation. HAT mechanism is more relevant to measure chain breaking capacity (Huang & Prior, 2005). The examples of assays that involve in HAT mechanism are oxygen radical absorbance capacity (ORAC), β-carotene/linoleic acid model system and inhibition of phospholipid peroxidation (Huang & Prior, 2005).

SET involves the mechanism of transferring one electron to reduce any compounds, including metals, carbonyls and radicals (Floegel *et al.*, 2011; Prieto *et al.*, 2015). The examples of assays involving SET are Folin-Ciocalteu (Folin-C), 2,2-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging, (TEAC) and ferric reducing ability of plasma (FRAP). However, Prior and Cao (2000) have classified DPPH, TEAC and Folin-C antioxidant assays into a category that utilises both SET and HAT reaction mechanisms, though predominantly based on electron transfer. A combination of several antioxidant assays could provide more reliable assessment of the antioxidant potential of the plant tested (Wang *et al.*, 2011).

2.5.2 Anti-wrinkle

The wrinkle inhibition effect could be acquired through the inhibition of specific key enzymes or biomarker such as collagenase, elastase and hyaluronidase which involve in skin aging process (Pimple & Badole, 2013). Human leukocyte elastase (or usually called human neutrophil elastase) cleaves the helix structure of type I collagen and degrade the elastic fibre on human skin (Masuda *et al*., 2009). Thus, the inhibition action towards elastase and collagenase, as well as hyaluronidase might possible induce the anti-wrinkle effects to the skin.

2.5.3 Anti-hyperpigmentation

Inhibitory effects of compound towards tyrosinase enzyme is reflection of controlling hyperpigmentation (Atta-ur-Rahman *et al.*, 2005). The tyrosinase inhibitor act by reversibly bind to tyrosinase and reduce its activity. The commonly used tyrosinase inhibitor is kojic acid, which is a fungal metabolite usually being used in cosmetic skin whitening and also used as food additive (Chang, 2009).

2.5.4 Cholinesterase inhibition

There are two classes of medication that have been approved by Food and Drug Administration (FDA), which are cholinesterase inhibitor (donepenzil, rivastigmine and galanthamine) and N-methyl-D-aspartate (NMDA) receptor antagonists (Salomone *et al.*, 2011). The treatment of AD by using the acetylcholinesterase (AChE) inhibitors seems to be a primary therapeutic strategies in Alzheimer disease prevention based on cholinergic hypothesis (Dey *et al.*, 2017; Yang *et al*., 2012). Acetylcholine is an important for cognition and memory, in which AD patients have low level of acetylcholine. Currently, the inhibition of AChE is the best option to improve cholinergic deficit by increasing the ACh level and ameliorate AD (Viegas *et al.*, 2005). There are two major categories of enzymes, which are AChE and butyrylcholinesterase (BuChE) which differed in substrate specificities and susceptibility to inhibitors. Thus, the inhibition of oxidation process and cholinesterase inhibition approach might be the best option to reduce the risk of this age-related neurodegenerative disease

2.6 Medicinal plant and anti-aging activities

In Asian countries, some herbs have been regarded as anti-aging herbs such as *Panax ginseng* and *Lycium barbarum* which displayed common properties. The characteristic of medicinal plants considered as anti-aging herbs are: (i) herbs that can help in increasing the energy level in body as the reduced level of energy is said to be caused by aging. These types of plants are usually clustered in tonifying herbs group. (ii) herbs that can act in flexible way (multistage intervention) by which it can act as food to accommodate essential nutrients when the body is in healthy stage, and also can intervene and relieving the symptoms of illneses, when disease occur. (iii) anti-aging herbs are multi targeted and can be used to treat several diseases. The therapeutic effects is achieved by modulating pathological aspects (Ho *et al.*, 2010).

2.6.1 Medicinal plants with antioxidant potential

Antioxidant originated from natural products such as plant is a cost effective and safe alternative to modify the damaging effect of oxidative stress (Pedrosa *et al*., 2016). The dietary intake rich in antioxidant could effectively reduce the deleterious effect of aging (Pandey & Rizvi, 2009). Several studies have showed that medicinal plants exert more antioxidant activity compared to the common dietary plants (Li *et al*., 2014).

A study on antioxidant and anti-aging potential of *Syzygium cumini*, *Trigonella foenum-graecum* and *Tinospora cordifolia* has showed that the plants with maximum antioxidant capacity possess the highest anti-aging properties measured by the accumulation of Lipofuscin. *Syzgium cumini,* locally known as Jamun in India shows maximum inhibition towards antioxidant activities measured by DPPH, ferric-reducing antioxidant power (FRAP) and lipid peroxidation assays.. The antioxidant capacity of the plants might be contributed by the hydrogen donating ability of flavonoids present in it (Dua & Srivastava, 2016). In another study, the antioxidant effect of polyherbal formulation was compared with single herb (Sindhuja *et al.*, 2014). Polyherbal formulation of *Tridax procumbens, Lantana camara*, *Euphorbia hirta* and *Thevetia peruviana* showed additive antioxidant capacity over its individual medicinal plants (Sindhuja *et al.*, 2014).

Herbal infusion of medicinal plants exhibit significant amount of antioxidant capacities. Li *et al*., (2014) have investigated the antioxidant capacities of herbal infusion from 223 medicinal plants by using FRAP, trolox equivalent antioxidant capacity (TEAC) and total phenolic content (TPC). TEAC and TPC showed significant correlation which indicates that phenolic compound in the herbal infusion might contribute to free radical scavenging activity. However, for FRAP assay, other phytochemical group might contribute to the activity as the weak correlation exist between FRAP and TPC.

The antioxidant capacity of plants may be influenced by genetic and environmental factors. *Annona muricata* leaves collected from different locality has shown the variation in the phytochemical content and antioxidant activity. The differences in the locality indicate that the plants were exposed to the different climate and environmental stress such as humidity, temperature and soil composition. The concentration of secondary metabolite is higher in stress environment (Najmuddin & Rahman, 2017). Thus, location of sampling is an important parameter that will influence the antioxidant capacity of medicinal plants.

2.6.2 Medicinal plants with anti-skin aging properties

2.6.2.1 Medicinal plants as anti-wrinkle agent

Skin could be protected by the action of plant extract through various mechanism such as by scavenging ROS molecules, rust inhibition, photoprotection, enzyme inhibition and prevent skin aging (Pedrosa *et al.*, 2016). Plant extracts have been shown to exhibit wound healing activities and act as anti-aging agent (Hong *et al*., 2014).

In traditional medicine, *Cassia fistula* flower has been used in Asian countries and Ayuverda to treat skin disease and wound healing. Experimental work has been done to validate the traditional claim. It was found that the *C. fistula* flower butanolic extract is able to increase collagen and hyaluronic acid syntheses in dose dependant manner *in vitro*. Other than that, the extract possess enzyme inhibition activity against collagenase, matrix metalloproteinase-2 (MMP-2) and tyrosinase enzymes. However, the flower extract did not show any effects towards the skin fibroblast cells (Limtrakul *et al*., 2016). These findings have validated the traditional use of *C. fistula* in the treatment of skin disorder

A study on anti-aging potential of Canadian forest species by Royer *et al.* (2013) indicated that the polyphenolic bark extracts have a potential to act as anti-aging agent. *Picea mariana*, *Pinus banksania*, *Abies balsamea*, *Betula alleghaniensis*, *Populus tremuloides* and *Acer rubrum* bark were investigated for the potential as nutraceutical, cosmaceutical and nutricosmetics agent. Green extraction method was applied for the samples by utilizing water and ethanol as solvents. The green extraction method is an extraction processes which would reduce the use of energy, allows use of alternative solvents and renewable natural products, and ensure a safe and high quality extract/product (Chemat, Vian, & Cravotto, 2012). It was found that all species gave positive result towards antioxidant, anti-enzyme and anti-microbial properties, which could be formulated for skin-care products (Royer *et al.*, 2013).

A study by Nema *et al.* (2013) on anti-aging potential of *Centella asiatica* showed that the extract exhibit anti-hyaluronidase and anti-elastase activity with IC_{50}

19.27 ± 0.37 mg/mL and 14.54 ± 0.39 mg/mL, respectively. The n-butanol fraction of *C. asiatica* also showed significant hyaluronidase and elastase inhibitory activities. Based on the HPLC analysis, the asiaticoside is the major compound that might contribute to the anti-aging activity of this plant (Nema *et al*., 2013). *Labisia pumila*, which is also known as women's plant exhibited the ability to protect the skin cells from photoaging. Herbal combination of *Punica granatum*, *Ginkgo biloba*, *Ficus carica* and *Morus alba* have showed positive effects to the collagenase inhibition activity. The combination of these fruits extract showed excellent antioxidative and anti-collagenase activity *in vitro* which comparable to the standard used (Ghimeray *et al*., 2015).

Different types of *Camellia sinensis* water extract (CSWE) have been investigated for the anti-wrinkle properties by using the photoaged hairless mouse model (Lee *et al.*, 2014). CSWE treated group have shown the improvement on the skin erythema index, moisture capacity and transepidermal water loss. The wrinkle measurement and image analysis observation also have shown that CSWE is able to inhibit wrinkle formation. In addition, CSWE diminished the epidermal thickness, increased the collagen and elastic fibre content, and reduced the expression of matrix metalloproteinase 3 (MMP-3). Interestingly, it was found that white and black tea have higher antiwrinkle activity compared to the green tea. Another *in vivo* study of medicinal plants, which is red ginseng extract on UV irradiated hairless mice showed that the supplementation of 2.5% red ginseng extract decreased the level of mRNA of procollagen type 1 and decreased the mRNA of protein levels of MMP-1 (Kang *et al*., 2009). All of the evidences indicate that certain medicinal plants have the ability to act as antiwrinkle agent.

2.6.2.2 Medicinal plants as anti-tyrosinase agent

Currently, the treatment of hyperpigmentation by using arbutin, hydroquinone, azelaic acid and kojic acid are associated with side effects eventhough it showed a positive result (Khan *et al.*, 2013). Melanin formation happens beneath the skin proceeds through a free radical mechanism, which could be disrupted by selective use of antioxidants, potent enough to poison this reaction (Momtaz *et al*., 2008). The level of antioxidant or tyrosinase inhibitory activities is proportional to the level of phenolic content (Hong *et al*., 2014).

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