CHAPTER 2

LITERATURE REVIEW

2.1 Cigarette smoke

Cigarette smoke is known to contain reactive peroxy radicals (**Church and Pryor, 1985; Pryor *et al.*, 1983**). Polymorphonuclear (PMN) leucocytes are another source of oxygen free radicals (**Fantone and Ward, 1982**)**.** Cigarette smoke can activate PMN leucocytes to produce oxygen free radicals through activated complement C5 (C5a). Activated complement C5 induces leucocyte chemotaxis, autoaggregation, increased adherence and oxygen free radicals generation (**Webster *et al.*, 1980; Craddock *et al.*, 1977**).

Cigarette smoke contains many toxic, carcinogenic, mutagenic, growth retardative and immunosuppressive compounds such as polycyclic aromatic hydrocarbons, cyanide, carbonmonoxide, lead, cadmium nitric oxide and nitric dioxide (**Brodie, 1994**). Also, the American tobacco industry is under pressured from the American congress to release a top secret list of another 599 chemicals to be added to cigarette smoke, including ammonia and insecticides (**Zickler, 2003**). These toxicity are often related to the nicotine content in cigarettes.

2.2 Smoke, nicotine and catecholamine neurotransmitters

2.2.1 Smoke and nicotine

Because of cigarette smoke contains over 4,000 chemicals that presents the toxic and carcinogenic affects in human body related to free radicals and nicotine (**Church and Pryor, 1985**). Approximately 20% to 25% of totally nicotine in a cigarette (1.8-3.25 mg per cigarette) can pass through the respiratory tract an absorbed into the blood circulation, can stimulate the adrenal medulla to induce the releasing of three catecholamine neurotransmitters such as adrenaline, noradrenaline and dopamine

(**Cryer *et al.*, 1976**). Some evidence reported that nicotine could enhance motivation during prolonged exercise (**O'Neill *et al.*, 1991**) and improves exercise endurance (**Mundel and David, 2006)**, but it also induces oxidative stress and chromosome aberration (**Wongwiwatthananukit, 2003**). But some previous evidences *in vivo* study showed some adverse effects of nicotine on inflammatory status and oxidative stress via activated NF-κB and apoptosis (**Crowley-Weber *et al.*, 2003**), including decreasing on glutathione (GSH) and increasing on malondialdehyde (MDA) (**Yildiz *et al.*, 1999**). Therefore, these findings are still controversial evidence on toxicity or side effects in human, especially on protein and lipid oxidation or DNA damage (**Kirkham *et al.*, 2004; Bloomer *et al.*, 2008; Alberg, 2002**).

2.2.2 Catecholamine neurotransmitter

Catecholamine is the principal neurotransmitter preferring to dopamine, noradrenaline and adrenaline that can mediate a variety of the central nervous system (CNS).

2.2.2.1 Dopamine is secreted in the central nervous system (CNS) and has many functions, such as motor control, cognition, emotion, memory processing and endocrine regulation (**Kobayashi, 2001**).

2.2.2.2 Adrenaline or epinephrine formed mostly in adrenal medulla is probably not metabolized to a significant extent prior to release into the blood stream (**Kopin, 1964**).

2.2.2.3 Noradrenaline or norepinephrine is fate of the intravenously injected catecholamine, therefore probably closely approximates the fate of adrenaline formed in the adrenal medulla and discharged into the adrenal vein (**Kopin, 1964**).

2.3 Pathway of catecholamine synthesis

Catecholamine is synthesized by the hydroxylation of phenylalanine to form tyrosine. After, the hydroxylation on phenolic group on tyrosine molecule, the catechol amino acid or 3, 4-dihydroxyphenylalanine (DOPA) is formed. Then 3, 4-dihydroxy-phenylamine (dopamine) is produced after decarboxylation on DOPA. Dopamine is well known as a catecholamine that found in several tissues, especially localized in relatively high concentration in the brain, e.g. basal ganglia. Dopamine is conversed to

noradrenaline in the adrenal medulla and it is generally accepted as the major transmitter substance released from sympathetic nerve endings. Finally, noradrenaline also can be methylated to be adrenaline.

The relative nonspecific four reactions that involve in the conversion of tyrosine to adrenaline, may permit the operation of a variety of minor alternative pathways in the formation of the catecholamines (**Figure 2.1**) (**Kopin, 1964**).

Normally, the brain is a feature in the release of dopamine neurotransmitter, involves happiness. Nicotine can bind to a nicotine receptor and directly effects on the dopamine level. Thus, maintaining dopamine level is related to smoking. In addition, nicotine also affects on releasing of other substances such as acetylcholine, serotonin, nor-epinephrine, glutamate, vasopressin, beta-endorphin and gamma-aminobutyric (GABA) (**Cryer *et al.*, 1976**). Nicotine is able to activate the sympathetic nervous system, which increases heart rate (HR) and blood pressure (BP) (**Irving and Yamamoto, 1963**), stroke volume (SV) and cardiac output (CO) (**Bargeron *et al.*, 1957**) and coronary blood flow (**Vezina *et al.*, 2007**).

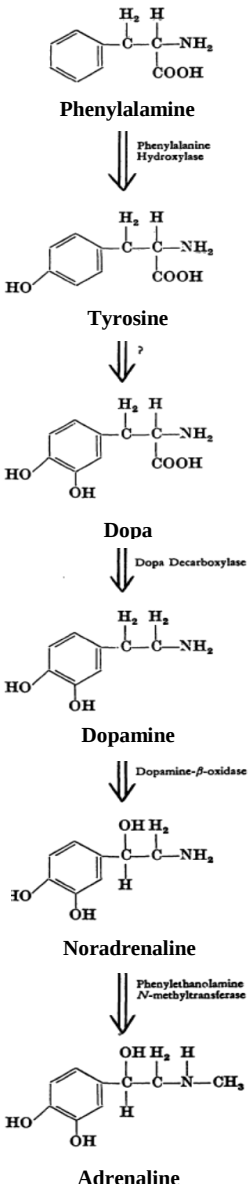

Figure 2.1 Pathway of catecholamine synthesis (**Modified from Kopin, 1964**)

2.4 Dopamine pathway

Figure 2.2 shows the dopamine pathway, in which the dopamine is a neurotransmitter or chemical messenger that activates several areas in the brain, as the substantia nigra and the ventral tegmental area (VTA). Then, the nucleus accumbens and frontal cortex, striatum are activated (**Arias-Carrion *et al.*, 2010; Pierce and Kumaresan, 2006).**

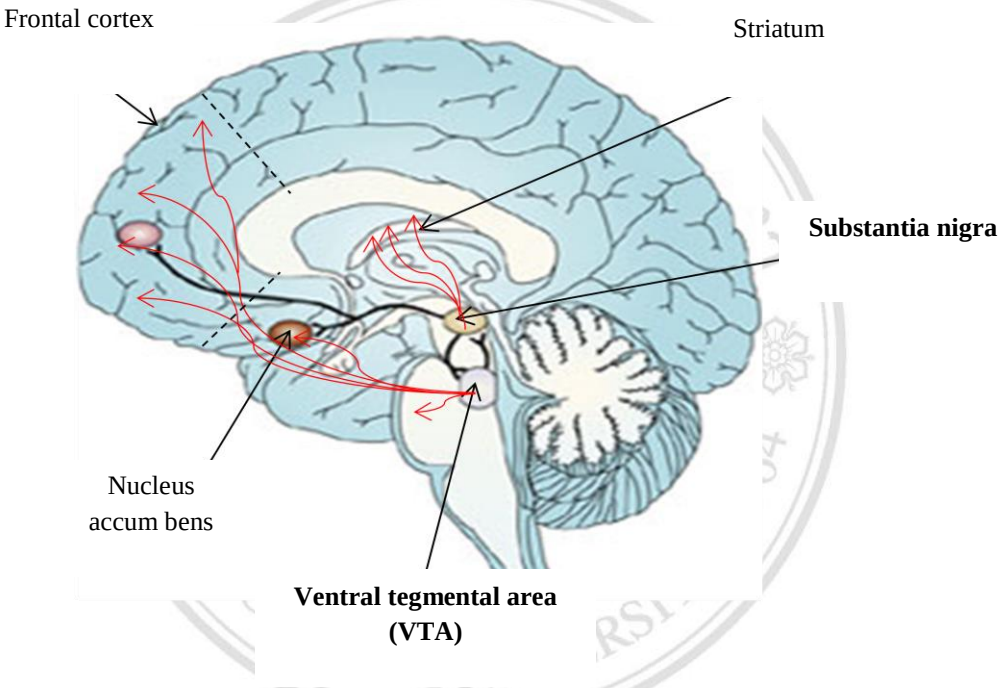

Figure 2.2 Dopamine pathways (**Modified from Agarwal, 2005**)

Dopamine is an important neurotransmitter affecting to the heart rate and blood pressure, as well as behavior and cognition, sexual performance, mood, learning capacity, sleep, memory, motivation, lactation and involuntary movement (**Benowitz *et al.*, 2002**).

2.5 Free radicals induced by smoking.

Cigarette smoke contains toxin components such as nicotine and tar. In addition, carbon monoxide (CO) is one such component effecting on the oxidative stress (**Valko *et al.*, 2007**). Oxidative stress can occur in the cell and relates to various pathogenesis of disease (**Droge, 2002**). However, under condition of oxidative stress in

overall cellular bimolecular are potential targets for reactive oxygen species (ROS) and reactive nitrogen species (RNS) (**Droge, 2002; Bielski, 1988**).

2.5.1 Reactive oxygen species (ROS) is free radical molecules that are increased under oxidative stress condition. The oxygen molecular is not reactive because of two paired electrons with parallel divides on the last electron sheath. Free radicals are derived from oxygen and more important in cell systems such as superoxide ($O_2^{\bullet -}$), hydroxyl radical ($OH^{\bullet}$), hydrogen peroxide (H_2O_2) and perhydroxyl radical ($HOO^{\bullet}$) (**Bielski, 1988**). Superoxide radical ($O_2^{\bullet -}$) is produced in mitochondria that reacts with ferric ion (Fe-III) to generate the ferrous ion (Fe-II) before catalysis the hydrogen peroxide (H_2O_2) to $OH^{\bullet}$, OH^- and Fe (III) (Figure 2.3).

$$O_2^{\bullet -} + \text{Fe (III)} \longrightarrow O_2 + \text{Fe (II)}$$

$$H_2O_2 + \text{Fe (II)} \longrightarrow OH^{\bullet} + OH^- + \text{Fe (III)}$$

Figure 2.3 Free radical propagation system from the fenton reaction or a metal-catalyzed Haber-Weiss reaction (**Nides *et al.*, 1994**).

2.5.2 Reactive nitrogen species (RNS) is classified in one of derived free radical molecules. A dominant type of RNS is nitric oxide (NO) in which is produced the some organisms by the oxidation of guanido-nitrogen atoms of L-arginine. This procedure is catalyzed by the nitric oxide synthase (NOS) enzyme and it can be converted to other RNS, especially peroxynitrite ($ONOO^-$) (**Droge, 2002; Bielski, 1988**).

2.6 Smoking cessation

Smoking cessation has been upgraded in developed and developing countries including Thailand. Although in some previous evidences show that behavioral counseling and/or pharmacotherapy have beneficials on long-term abstinence (**Stead *et al.*, 2008; Halliwell, 1993**), but the major disadvantages of this approach such as high cost and unwanted side effects with nausea, dry mouth, weight gain and sedation (**Chea *et al.*, 2006**) are presented.

2.7 Pharmacotherapy with nicotine replacement therapy (NRT)

2.7.1 Varenicline tartarate is a selective nicotinic receptor, partial agonist. From the results of a multicenter phase II study with a double blind trial by comparing the varenicline, placebo and bupropion, showed that both drugs presented the same efficacy and tolerability, but some side effects as nausea, vomiting, headache and insomnia were also documented (**Dong and Blier, 2001**).

2.7.2 Bupropion HCl is used to treat for major depressive disorder and seasonal affective disorder. It is used to help people to stop smoking by reducing cravings and other withdrawal effects. Side effects of this medication are presented as common early symptoms such as nausea, insomnia and dry mouth that has suggested the mechanism from the inhibition of neural reuptake of dopamine or noradrenaline (**Fiore *et al.*, 2000; Wagena *et al.*, 2005**).

2.7.3 Nortriptyline is the main active metabolite of amitriptyline with longer half-life ($t^1_{/2}$) than the parent compound. Nortriptyline undergoes extensive first pass metabolism in the liver to active compound 10-hydroxy nortriptyline. In a meta-analysis of 5 trials, comprising in 61 smokers, it concluded that nortriptyline had higher prolong abstinence rate at 6 months as compared to the placebo. Therefore, this drug has a well tolerate and can be used as a first line drug in smoking cessation, considering its efficacy and low cost (**Dickerson and Carek, 2002**). However, a previous randomized trial study on the efficacy of nortriptyline, also found the adverse effects with dry mouth (38%) and sedation (20%) (**Dickerson and Carek, 2002**).

2.7.4 Clonidine can be applied to reduce withdrawal symptoms and has approximately doubles abstinence rate when compared to a placebo. But its side effects as dry mouth, sedation and abruptly when stopped the drug were also presented in previous studies (**Stead *et al.*, 2008; Gamble, 1957; Gourlay *et al.*, 2004**).

2.8 Herb or natural plants

Some types of herbs such as Peep, Shallot, Snow lotus and *Vernonia cinerea* Less. has reported the ability to reduce or stop smoking.

2.8.1 Peep (*Millingtonia hortensis* Linn.)

Peep is known commonly as cork tree, Akas nim and Nim chameli. It is an important medicinal plant in Southern Asia; ranging through India, Burma, Thailand and southern China. The stem bark is used traditionally as mainly a lung tonic, anti-asthmatic and antimicrobial. The scientific activities that have been reported so far from this plant are anti-fungal, anti-oxidant and anti-proliferative activities (**Abirami and Rajendran, 2012**).

2.8.2 Shallot *(Allium ascalonicum* Linn.)

Shallot is commonly called as a spring onion, and is a member of the *Liliaceae* family that also an annual herbaceous plant widely found in Nigeria. This plant is used widely for flavoring food, which has been used mainly as a traditional spice from ancient times. It has many various benefits; for instance, anti-bacterial, anti-fungal property, antioxidant capacity and peroxynitrite-scavenging capacity (**Amin and Kapadnis, 2005; Ho *et al.*, 2010; Law and Salick, 2005**).

2.8.3 Snow lotus (*Saussurea laniceps.*)

Snow lotus that is classified into the *Asteraceae* family, has more than 300 species. It has been used in traditional Chinese and Tibetan medicine for the treatment of headaches, high blood pressure and menstrual problems (**Bunyapraphatsara, 2005**).

2.8.4 *Vernonia cinerea* Less. (VC)

VC is a natural plant that can be found in many areas around the world. It is classified in the *Asteraceae* family. Dominantly characteristic of VC is a slender stemmed plant, variable leaf shape and pinkish-purple flowers. VC is a perennial herbaceous plant, distributed in grassy areas in Southeast Asia and Hawaii **(Lin, 2005; Lhieochaiphant, 1985; Lee *et al.*, 2005).**

Figure 2.4 Characteristic of *Vernonia cinerea* Less.

From previous documented and recommended on pharmacological function, VC can relief on asthma, cough, fever, malaria, urinary calculi, and arthritis and it also helps to stop smoking **(Chea *et al.*, 2006).** In a previous study in 32 human smokers at the smoking cessation clinic at the Thanyarak Institute, Pathumthani, Thailand with a randomized, single-blind controlled trial (**Wongwiwatthananukit, 2003**), administration of VC tea at 150 mL for 3 times daily, 14 days could reduce the smoking rate, due to the change of taste and cigarette smell (**Halliwell, 1993**). But no any reports to represent its mechanism on stop smoking in human. Moreover, the study of Leelarungrayub and co-workers (2011) on the VC supplementation with condense juice with or without exercise in active smoker, showed that active smokers could stop smoking quickly; moreover, beta-endorphin and oxidative stress in plasma were improved after 14 days supplementation (**Leelarungrayub *et al.*, 2011**). Therefore, the preparative protocol of VC plant with a condense juice is very interesting and possibly more potential effect on stop smoking than a tea bag.

So anyway, there have some beneficial evidences about VC activity in animal studies; for example, anti-inflammatory, analgesic, antipyretic activities in mouse (**Misra *et al.*, 1984**) and the adjuvant-induced arthritis (**Latha *et al.*, 1998**). Furthermore, some active compounds as flavonoid, terpenoid, steroids, saponins,

alkaloids, carbohydrates, phenols, tanins and proteins were presented (**Latha *et al.*, 1998**). Including, the major compounds as N-hexadecanoic acid (42.88%), 1, 2-benzene-dicarboxylic acid (23%), squalence (11.31%), caryophyllene oxide (2.31%), guaiol (1.75%), octadecanoic acid (4.41%) and 9, 12-octadecanoic (9.38%) in methanolic extract were found (**Amin and Kapadnis, 2005**). Therefore, these reviewed evidences can be summarized the antioxidant and anti-inflammatory activity in VC plant from methanol extraction, including the interested active compounds, but cannot be concluded in the VC condensed preparation, especially relating to neurotransmitters or toxicity that were the aims in this study.